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International application number: PCT/US04/024387

International filing date: 18 August 2004 (18.08.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/496,537
Filing date: 20 August 2003 (20.08.2003)

Date of receipt at the International Bureau: 06 September 2004 (06.09.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

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APPLICATION NUMBER: *60/496,537*
FILING DATE: *August 20, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/24387*

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

Docket Number	P-16292	Type a plus sign (+) inside this box -->	+

INVENTOR(s)/APPLICANT(s)			
LAST NAME	FIRST NAME	MIDDLE NAME	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
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TITLE OF THE INVENTION (280 characters max)

Compounds, Methods and Formulations for the Oral Delivery of a Glucagon Like Peptide (GLP)-1 Compound

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ENCLOSED APPLICATION PARTS (*check all that apply*)

- [X] Specification — Number of pages: 73
- [ ] Drawing(s) — Number of Sheets:
- [ ] Small Entity Statement
- [ ] Other (Specify)

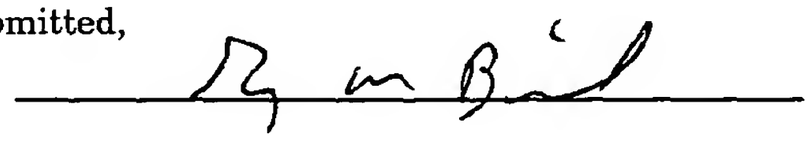
METHOD OF PAYMENT (*check one*)

- [ ] A check or money order is enclosed to cover the Provisional filing fees
- [X] The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: 05-0840

PROVISIONAL FILING FEE AMOUNT ($): $160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- [X] No.
- [ ] Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,
SIGNATURE 
Date 08 / 20 / 2003

TYPED or PRINTED NAME GARY M. BIRCH

REGISTRATION NO. (*if appropriate*) 48,881

- [ ] Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FOR PATENT FILING ONLY

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Queen Thomas — Signature

P-16292

COMPOUNDS, METHODS AND FORMULATIONS FOR THE ORAL DELIVERY OF A GLUCAGON LIKE PEPTIDE (GLP)-1 COMPOUND

FIELD OF THE INVENTION

The present invention relates to novel compounds, methods, and formulations useful for the oral administration of a GLP-1 compound. The compounds of the present invention are useful for forming a mixture with a GLP-1 compound for the oral administration of the mixture to an animal.

BACKGROUND OF THE INVENTION

Conventional means for delivering active agents are often severely limited by biological, chemical, and physical barriers. Typically, these barriers are imposed by the environment through which delivery occurs, the environment of the target for delivery, or the target itself. Biologically or chemically active agents are particularly vulnerable to such barriers. In the delivery to animals of biologically active or chemically active pharmacological and therapeutic agents, physical and chemical barriers are imposed by the body. Examples of physical barriers are the skin and various organ membranes that must be traversed before reaching a target, and examples of chemical barriers include, but are not limited to, variations in pH, lipid bilayers, and degrading enzymes.

These barriers are of particular significance in the design of oral delivery systems. Oral delivery of many biologically or chemically active agents would be the route of choice for administration to animals if not for biological, chemical, and physical barriers such as varying pH in the gastrointestinal (GI) tract, powerful digestive enzymes, and active agent impermeable gastrointestinal membranes. Among the numerous agents

which are not typically amenable to oral administration are biologically or chemically active peptides, such as calcitonin and insulin; polysaccharides, and in particular mucopolysaccharides including, but not limited to, heparin; heparinoids; antibiotics; and other organic substances. These agents are rapidly rendered ineffective or are destroyed in the gastrointestinal tract by acid hydrolysis, enzymes, or the like.

Earlier methods for orally administering vulnerable pharmacological agents have relied on the co-administration of excipients or enhancers (e.g., resorcinols and non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of enzyme inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate) to inhibit enzymatic degradation.

Liposomes have also been described as drug delivery systems for insulin and heparin. See, for example, U.S. Pat. No. 4,239,754; Patel et al (1976), FEBS Letters, Vol 62, pg. 60, and Hashimoto et al. (1970), Endocrinology Japan, Vol, 26, pg. 337.

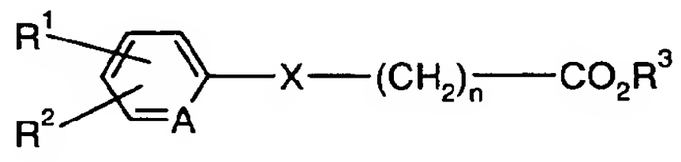
However, broad spectrum use of such drug delivery systems is precluded because: (1) the systems require toxic amounts of excipients, enhancers or inhibitors; (2) suitable low molecular weight cargos, i.e. active agents, are not available; (3) they exhibit poor stability and inadequate shelf life; (4) the systems are difficult to manufacture; (5) the systems fail to protect the active agent (cargo); (6) the systems adversely alter the active agent; or (7) the systems fail to allow or promote absorption of the active agent.

More recently, microspheres of artificial polymers of mixed amino acids (proteinoids) have been used to deliver pharmaceuticals. For example, U.S. Pat. No. 4,925,673 describes drug-containing proteinoid microsphere carriers as well as methods for their preparation and use. These proteinoid microspheres are useful for the delivery of a number of active agents.

Delivery agent molecules have also been disclosed in U.S. Patent Nos. 5,541,155; 5,693,338; 5,976,569; 5,643,957; 5,955,503; 6,100,298; 5,650,386; 5,866,536; 5,965,121; 5,989,539; 6,001,347; 6,071,510; 5,820,881; and 6,242,495; *see also* WO 02/02509; WO 01/51454; WO 01/44199; WO 01/32130; WO 00/59863; WO 00/50386; WO 00/47188; and WO 00/40203.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to compounds of formula I



I

wherein

R^1 and R^2 are each independently H, OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, halo or $NR^4R^{4'}$;

R^3 is H, C_1-C_6 alkyl;

R^4 is H, COR^5, SO_2R^6, or C_1-C_6 alkyl;

$R^{4'}$ is H or C_1-C_6 alkyl;

R^5 is H or C_1-C_6 alkyl;

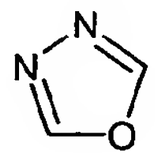
R^6 is H or C_1-C_6 alkyl;

A is C or N;

X is a 5 membered aromatic heterocycle wherein said heterocycle contains at least two or three heteroatoms selected from N, S and O wherein at least one heteroatom must be N;

n is 2, 3, 4, 5, 6 or 7;

provided that when X is



,

then A is N;

or a pharmaceutical salt thereof.

The present invention also relates to a pharmaceutical composition containing a compound of formula I, or a pharmaceutical salt thereof, and a GLP-1 compound.

The present invention also relates to pharmaceutical formulation containing a compound of formula I, or a pharmaceutical salt thereof, a GLP-1 compound, and a pharmaceutical carrier.

DETAILED DESCRIPTION OF THE INVENTION

Reference hereafter to "a compound of formula I" includes the pharmaceutical salts thereof.

The compounds of formula I are useful for increasing the oral bioavailability of an active agent, i.e., a GLP-1 compound, when said compound is mixed with the active agent to form a combination composition. Said combination is one embodiment of the present invention. The compositions of the present invention comprise a compound of formula I, that is, a delivery agent, and a GLP-1 compound.

The present invention is particularly advantageous for delivering a GLP-1 compound that would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone (i.e. the area in which the active agent of the delivery composition is to be released) and within the body of the animal to which it is administered. The compositions comprising one or more compounds of formula I and a GLP-1 compound have utility in the delivery of said GLP-1 compound to selected biological systems and in an increased or improved bioavailability of the GLP-1 compound compared to administration of the active agent without the delivery agent. Delivery can be improved by delivering more active agent over a period of time, or in delivering active agent in a particular time period (such as to effect quicker or delayed delivery) or over a period of time (such as sustained delivery).

For the purposes of the present invention, as disclosed and claimed herein, the following terms are defined below.

The term "halo" refers to fluoro, chloro, bromo and iodo. The term "C_1-C_6 alkyl" represents a straight, branched or cyclic hydrocarbon moiety having from one to six carbon atoms, *e.g.*, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl and the like. Moieties such as a cyclobutylmethylene are also included within the scope of a C_1-C_6 alkyl group.

The term "C_1-C_4 alkyl" refers specifically to methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclopropylmethyl, n-butyl, isobutyl, sec-butyl, t-butyl and cyclobutyl. A "C_1-C_6 alkoxy" group is a C_1-C_6 alkyl moiety connected through an oxy linkage.

The term "GLP-l compound" as used herein refers to one or more naturally occurring GLP-1 polypeptides (GLP-1(7-37)OH and GLP-1(7-36)NH_2), GLP-1 fragments, GLP-l analogs, GLP-1 derivatives of naturally occurring GLP-l polypeptides, GLP-1 fragments, or GLP-l analogs, and Exendin-3 and Exendin-4 that have the ability to bind to the GLP-1 receptor and initiate a signal transduction pathway resulting in insulinotropic activity as described in PCT Application Number PCT/US03/03111 and herein incorporated by reference.

Preferred Compounds (Embodiments) of the Invention

Certain compounds of the invention are particularly interesting and are preferred. The following listing sets out several groups of preferred compounds. It will be understood that each of the listings may be combined with other listings to create additional groups of preferred compounds.

R^1 and R^2 are each independently H, OH, OCH_3 CH_3, CF_3, Cl, or Br;

R^4 is H;

R^4 is COR^5 and R^5 is CH_3;

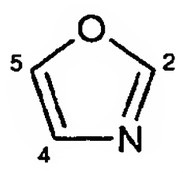
R^4 is SO_2R^6 and R^6 is CH_3;

$R^{4'}$ is H;

A is CH;

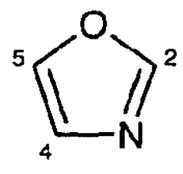
A is N;

X is



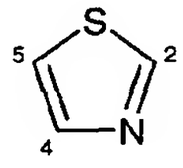
and the phenyl substituent is attached at carbon atom number 4 and the alkanoic acid chain is attached at carbon atom number 2;

X is



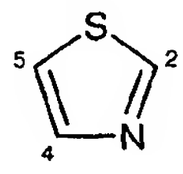
and the phenyl substituent is attached at carbon atom number 5 and the alkanoic acid is attached at carbon atom number 2;

X is



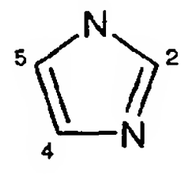
and the phenyl substituent is attached at carbon atom number 4 and the alkanoic acid is attached at carbon atom number 2;

X is



and the phenyl substituent is attached at carbon atom number 5 and the alkanoic acid is attached at carbon atom number 2;

X is

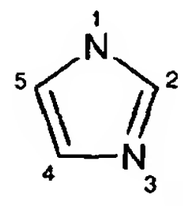


and the phenyl substituent is attached at either carbon atom number 4 or 5 and the alkanoic acid is attached at carbon atom number 2;

X is

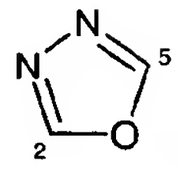
and the phenyl substituent is attached at carbon atom number 5 and the alkanoic acid is attached at nitrogen atom number 3;

X is



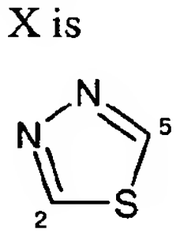
and the phenyl substituent is attached at carbon atom number 2 and the alkanoic acid is attached at either nitrogen atom number 1 or number 3;

X is



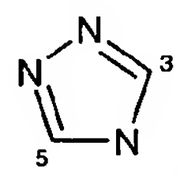
and the phenyl substituent is attached at carbon atom number 5 and the alkanoic acid is attached at carbon atom number 2;

X is



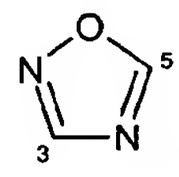
and the phenyl substituent is attached at carbon atom number 5 and the alkanoic acid is attached at carbon atom number 2;

X is



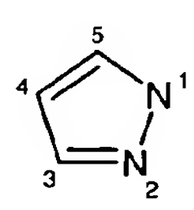
and the phenyl substituent is attached at carbon atom number 5 and the alkanoic acid is attached at carbon atom number 3;

X is



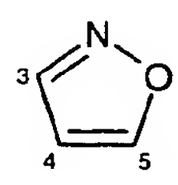
and the phenyl substituent is attached at carbon atom number 3 and the alkanoic acid is attached at carbon atom number 5;

X is



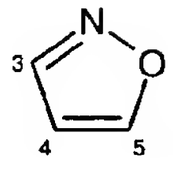
and the phenyl substituent is attached at carbon atom number 3 and the alkanoic acid is attached at nitrogen atom number 1;

X is



and the phenyl substituent is attached at carbon atom number 3 and the alkanoic acid is attached at carbon atom number 5;

X is



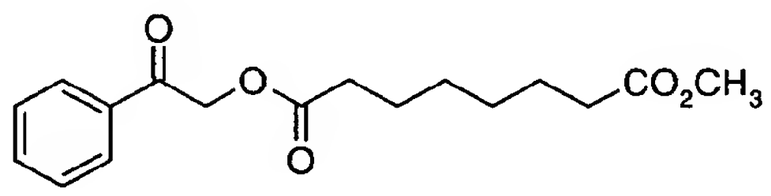
and the phenyl substituent is attached at carbon atom number 3 and the alkanoic acid is attached at carbon atom number 4.

Preparations and Examples

All non-aqueous reactions were performed under a dry atmosphere of nitrogen unless otherwise specified. Commercial grade reagents and anhydrous solvents were used as received from vendors and no attempts were made to purify or dry these components further. Removal of solvents under reduced pressure was accomplished with a Buchi rotary evaporator at approximately 28 mm Hg pressure using a Teflon-lined KNF vacuum pump. Thin layer chromatography was performed using 1" x 3" Analtech No. 02521, Whatman No. MK6F or EM Science No. 5719-2 silica gel plates with fluorescent indicator. Visualization of TLC plates was made by observation with either short wave UV light, 10% phosphomolybdic acid in ethanol or in iodine vapors. Flash column chromatography was carried out using Kieselgel silica gel 60. Proton NMR spectra were obtained on a Bruker AC 300 MHz Nuclear Magnetic Resonance Spectrometer and are reported in ppm δ values, using tetramethylsilane as an internal reference. Melting points were obtained using an Electrothermal melting point apparatus and are uncorrected. CI Mass spectroscopic analyses were performed on a Shimadzu QP-5000 GC/Mass Spectrometer (methane) by direct injection. API Mass spectroscopic analyses were performed on a Finnegan LCQ Duo Ion Trap or a PESciex API 150EX mass spectrometer, using electro spray ionization (ESI) or atmospheric pressure chemical ionization (APCI). HPLC analyses were conducted using a Waters Symmetry C18, 5um, WAT046980, 3.9x150 mm column. The elution system consisted of 90:10 (0.1% TFA in H_2O)/(0.1% TFA in CH_3CN) gradient elution to 10:90 (0.1% TFA in H_2O)/(0.1% TFA in CH_3CN) over 20 min, followed by 10:90 (0.1% TFA in H_2O)/(0.1% TFA in CH_3CN) isocratic elution for 10 min, followed by 90:10 (0.1% TFA in H_2O)/(0.1% TFA in CH_3CN) isocratic elution for 10 min. The flow rate was 1 mL/min. UV Detection was performed at both 214 and 254 nm.

Preparation 1

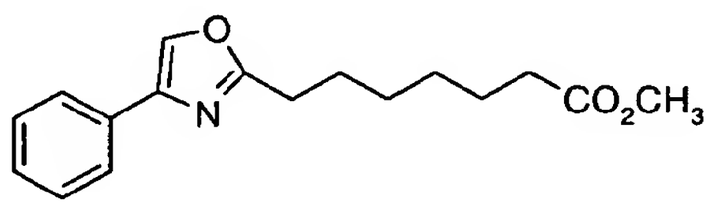
Octanedioic Acid Methyl Ester 2-Oxo-2-phenylethyl Ester



Add a solution of sodium bicarbonate (2.12 g, 25.2 mmol) in water (10 mL) to a solution of commercially available suberic acid monomethyl ester (4.75 g, 25.2 mmol) in methanol (50 mL) at room temperature and stir the mixture for 30 minutes. Remove the solvent under reduced pressure and add the residue to a solution of commercially available 2-bromoacetophenone (5.0 g, 25.1 mmol) in acetone (150 mL) at room temperature under nitrogen. Heat the mixture at reflux for 10 hours and then remove the solvent under reduced pressure. Dilute the residue with diethyl ether (300 mL), stir for 20 minutes, filter through a short silica gel column, and wash with diethyl ether (2 x 50 mL). Remove the solvent under reduced pressure to provide octanedioic acid methyl ester 2-oxo-2-phenylethyl ester (6.9 g, 90%) as an oil.

Preparation 2

7-(4-Phenyloxazol-2-yl)heptanoic Acid Methyl Ester

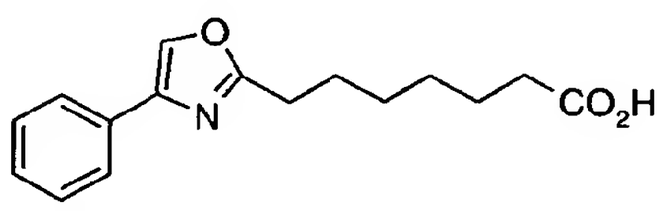


Heat a mixture of octanedioic acid methyl ester 2-oxo-2-phenylethyl ester (Preparation 1, 6.93 g, 22.6 mmol), acetamide (6.75 g, 114 mmol) and boron trifluoride diethyl etherate (3.0 mL, 23.7 mmol) at 135-140°C under nitrogen for 4 hours. Cool the mixture, dilute with saturated $NaHCO_3$ solution (100 mL), and extract with ethyl acetate (250 mL). Wash the organic extract with 100 mL of saturated aqueous sodium chloride

(brine) and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (85:15), to provide 7-(4-phenyloxazol-2-yl)heptanoic acid methyl ester (5.7 g, 88%) as an oil.

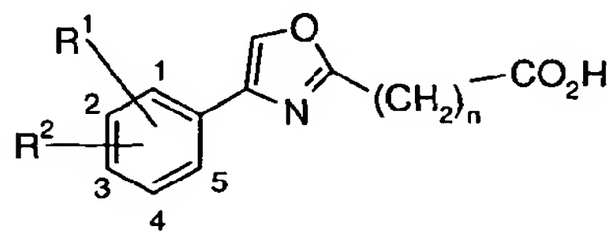
Example 1

7-(4-Phenyloxazol-2-yl)heptanoic Acid



Add solution of sodium hydroxide (1.60 g, 40.0 mmol) in water (30 mL) to a solution of 7-(4-phenyloxazol-2-yl)heptanoic acid methyl ester (Preparation 2, 5.75 g, 20.0 mmol) in methanol (40 mL) at room temperature and heat the mixture at 40°C for 2 hours. Adjust the pH of the mixture to 2 with 1 N HCl and extract with ethyl acetate (600 mL). Wash the organic extract with water (3 x 150 mL), dry over sodium sulfate and remove the solvent under reduced pressure. Triturate the residue with hexanes/ethyl acetate and collect the solids by filtration to provide 7-(4-phenyloxazol-2-yl)heptanoic acid (5.01 g, 91%) as a white solid: APCI mass spectrum *m/z* 272 $[C_{16}H_{19}NO_3 - H]^-$.

Prepare Examples 2-11, compounds of formula I(a) and Table 1 below, by the same process as in the preparation of Example 1.



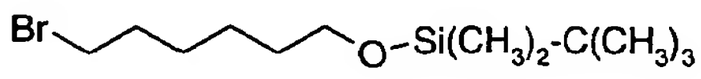
I(a)

Table 1: Compounds of formula I(a)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
2	OCH_3 (1)	H	3	261 $[C_{14}H_{15}NO_4]^+$
3	OCH_3 (1)	H	4	276 $[C_{15}H_{17}NO_4 + H]^+$
4	OCH_3 (1)	H	5	290 $[C_{16}H_{19}NO_4 + H]^+$
5	OH (1)	H	4	260 $[C_{14}H_{15}NO_4 - H]^-$
6	OH (1)	OCH_3 (3)	4	290 $[C_{15}H_{17}NO_5 - H]^-$
7	OCH_3 (1)	H	6	302 $[C_{17}H_{21}NO_4 - H]^-$
8	H	OCH_3 (3)	6	302 $[C_{17}H_{21}NO_4 - H]^-$
9	OH (1)	H	6	288 $[C_{16}H_{19}NO_4 - H]^-$
10	OH (1)	OCH_3 (3)	6	318 $[C_{17}H_{21}NO_5 - H]^-$
11	OH (1)	Cl (4)	6	322 $[C_{16}H_{18}ClNO_4 - H]^-$

Preparation 3

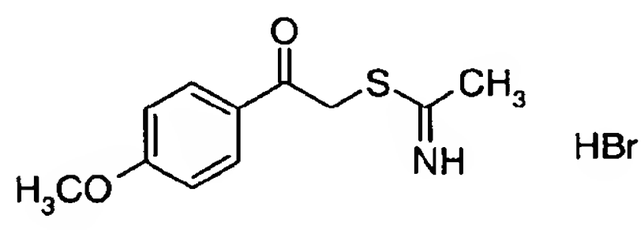
(6-Bromohexyloxy)-*tert*-butyldimethylsilane



Add a solution of *tert*-butyldimethylsilyl chloride (5.0 g, 33.1 mmol) in dimethylforamide (DMF) (70 mL) dropwise over 15 minutes to a solution of commercially available 6-bromohexanol (5.0 g, 27.6 mmol) and imidazole (4.7 g, 69 mmol) in DMF (80 mL) at 0°C under nitrogen protection and stir the mixture for another 3.5 hours. Dilute the mixture with water (400 mL) and extract with diethyl ether (3 x 150 mL). Dry the combined organic extracts over sodium sulfate and remove the solvent under reduced pressure. Purify the crude product by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:19), to provide (6-bromohexyloxy)-*tert*-butyldimethylsilane (8.05 g, 98%) as an oil.

Preparation 4

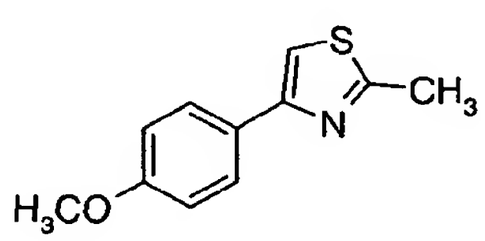
Thioacetimidic Acid 2-(4-Methoxyphenyl)-2-oxoethyl Ester Hydrobromide



Add a solution of thioacetamide (2.65 g, 34.9 mmol) in acetone (100 mL) dropwise to a solution of 2-bromo-4'-methoxyacetonephenone (8.0 g, 34.9 mmol) in acetone (100 mL) at room temperature under nitrogen. Stir the mixture for 12 hours. Collect the solids by filtration and wash with cold acetone (30 mL) to provide thioacetimidic acid 2-(4-methoxyphenyl)-2-oxoethyl ester hydrobromide (10.25 g, 96%) as a white power.

Preparation 5

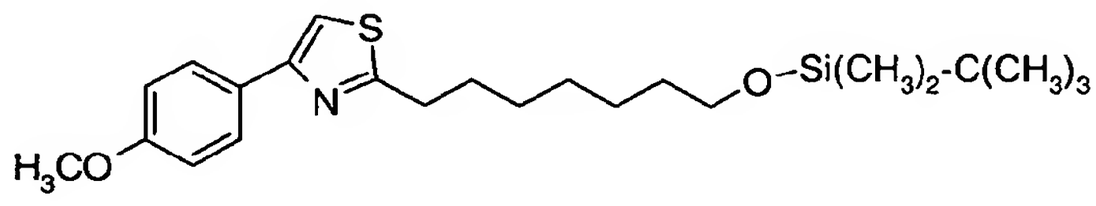
4-(4-Methoxyphenyl)-2-methylthiazole



Heat a mixture of thioacetimidic acid 2-(4-methoxyphenyl)-2-oxoethyl ester hydrobromide (Preparation 4, 10.0 g, 32.9 mmol) and zinc (II) chloride (4.50 g, 33.0 mmol) in methanol (80 mL) at reflux under nitrogen protection for 6.5 hours. Cool the mixture, slowly dilute with saturated $NaHCO_3$ (300 mL), and extract with methylene chloride (400 mL x 2). Dry the combined organic extracts over sodium sulfate and remove the solvent under reduced pressure. Purify the crude product by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (9:1), to provide 4-(4-methoxyphenyl)-2-methylthiazole (6.24 g, 92%) as a white powder: APCI mass spectrum *m/z* 206 $[C_{11}H_{11}NOS + H]^+$.

Preparation 6

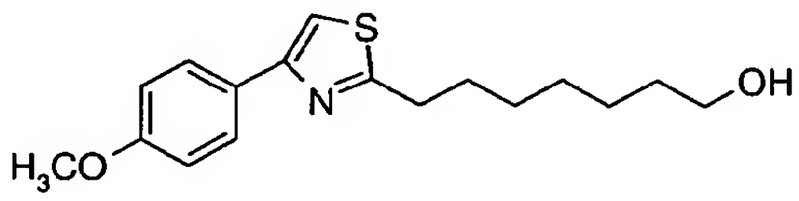
2-[7-(*tert*-Butyldimethylsilanyloxy)heptyl]-4-(4-methoxyphenyl)thiazole



Add a solution of *tert*-butyllithium (26.35 mmol, 15.5 mL, 1.7 M in hexanes) dropwise to a solution of 4-(4-methoxyphenyl)-2-methylthiazole (Preparation 5, 6.15 g, 29.9 mmol) in degassed anhydrous tetrahydrofuran (THF) (100 mL) at -78°C under nitrogen and stir the solution for 45 minutes. To this solution, add a solution of (6-bromohexyloxy)-*tert*-butyldimethylsilane (Preparation 3, 7.20 g, 24.4 mmol) over 5 min and stir the mixture for 2 hours. Warm the mixture to 0°C, dilute with NH_4Cl (200 mL) and brine (250 mL) and extract with methylene chloride (3 x 150 mL). Dry the combined organic extracts over magnesium sulfate and remove the solvent under reduced pressure. Purify the crude product by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (5:1), to provide 2-[7-(*tert*-butyldimethylsilanyloxy)heptyl]-4-(4-methoxyphenyl)thiazole (6.27 g, 50%) as a viscous oil.

Preparation 7

7-[4-(4-Methoxyphenyl)thiazol-2-yl]heptan-1-ol

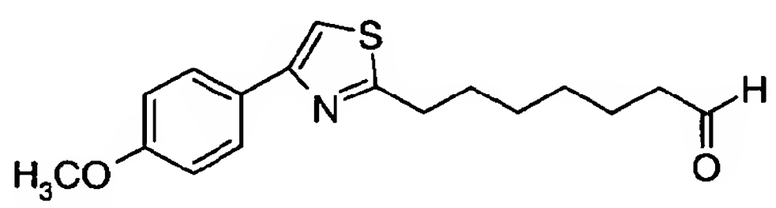


Add a solution of 1 N tetra-*n*-butylammonium fluoride (25.0 mmol, 25 mL, 1 M solution in THF) dropwise over 10 minutes to a solution of 2-[7-(*tert*-butyldimethylsilanyloxy)heptyl]-4-(4-methoxyphenyl)thiazole (Preparation 6, 6.27 g, 14.9 mmol) in anhydrous THF (50 mL) at 0°C under nitrogen and stir the mixture for 30

minutes at 0°C and then stir at room temperature for 3 hours. Dilute the mixture with brine (150 mL) and extract with ethyl acetate (100 mL x 3). Dry the combined organic extracts over magnesium sulfate and remove the solvent under reduced pressure. Purify the crude product by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:2), to give 7-[4-(4-methoxyphenyl)thiazol-2-yl]heptan-1-ol (4.07 g, 89%) as a solid: APCI mass spectrum *m/z* 306 $[C_{17}H_{23}NO_2S + H]^+$.

Preparation 8

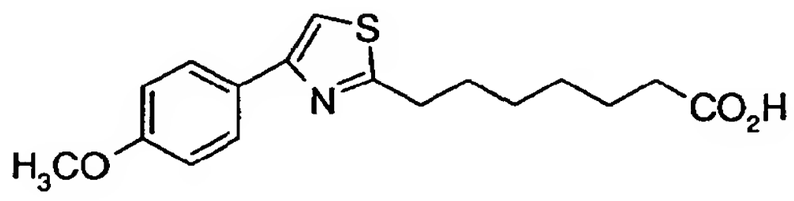
7-[4-(4-Methoxyphenyl)thiazol-2-yl]heptanal



Add anhydrous dimethyl sulfoxide (0.25 mL, 3.52 mmol) dropwise over 2 minutes to a solution of oxalyl chloride (393 mg, 3.10 mmol) in methylene chloride (10 mL) at -78°C under nitrogen and stir the mixture for 20 minutes. Add a solution of 7-[4-(4-methoxyphenyl) thiazol-2-yl]heptan-1-ol (Preparation 7, 0.609 g, 1.99 mmol) in methylene chloride (10 mL) dropwise in 5 minutes and then stir the mixture for 30 minutes. To this mixture, add triethylamine (1.0 mL, 7.2 mmol), stir and warm the reaction mixture to room temperature for 40 minutes. Dilute the mixture with ethyl acetate (100 mL), wash with brine (3 x 30 mL), dry over sodium sulfate and remove the solvent under reduced pressure to provide 7-[4-(4-methoxyphenyl)thiazol-2-yl]heptanal (0.6 g, 99%) as a solid: APCI mass spectrum *m/z* 304 $[C_{17}H_{21}NO_2S + H]^+$.

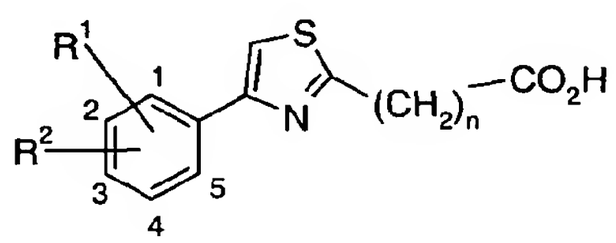
Example 12

7-[4-(4-Methoxyphenyl)thiazol-2-yl]heptanoic Acid



Add 2-methyl-2-butene (7.0 mL) and sodium hypochlorite (2.51 g, 27.75 mmol) to a solution of 7-[4-(4-methoxyphenyl)thiazol-2-yl]heptanal (Preparation 8, 4.02 g, 13.25 mmol) and potassium dihydrogen phosphate (3.10 g, 22.78 mmol) in *tert*-butanol (60 mL) and water (12 mL) at room temperature. Stir the mixture for 40 minutes, dilute with ethyl acetate (500 mL) and wash with brine (3 x 200 mL). Dry the combined organic extracts over sodium sulfate and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with methanol/methylene chloride (1:19), and triturate the residue with hexanes/methylene chloride to afford 7-[4-(4-methoxyphenyl)thiazol-2-yl]heptanoic acid (3.91 g, 88%) as a solid: APCI MS *m/z* 320 $[C_{17}H_{21}NO_3S + H]^+$.

Prepare Examples 13 and 14, compounds of formula I(b) and Table 2 below, by the same process as in the preparation of Example 12.



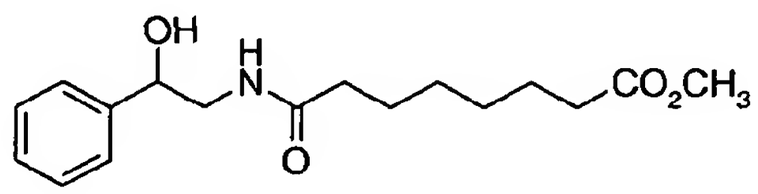
I(b)

Table 2: Compounds of formula I(b)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
13	OCH_3 (1)	H	6	318 $[C_{17}H_{21}NO_3S - H]^-$
14	OH (1)	H	6	304 $[C_{16}H_{19}NO_3S - H]^-$

Preparation 9

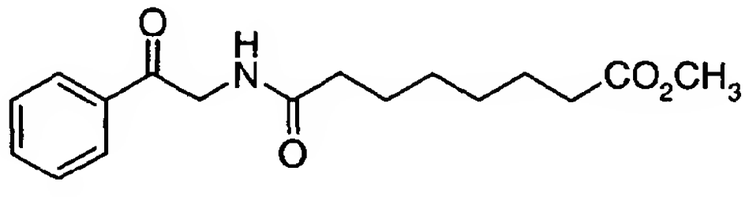
7-(2-Hydroxy-2-phenylethylcarbamoyl)heptanoic Acid Methyl Ester



Add 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide(EDC) (8.5 g, 44.3 mL) to a solution of commercially available 2-amino-1-phenylethanol (5.0 g, 36.4 mmol), commercially available suberic acid monomethyl ester (6.85 g, 36.4 mmol) and 1-hydroxybenzotriazole (HOBt,5.0 g, 37.0 mmol) in THF (200 mL) at room temperature under nitrogen. Stir the mixture for 12 hours. Dilute the mixture with ethyl acetate (600 mL), wash with 1N HCl (2 x 150 mL), brine (2 x 150 mL), $NaHCO_3$ (2 x 150 mL) and brine (150 mL) solutions and dry over sodium sulfate. Remove the solvent under reduced pressure to provide 7-(2-hydroxy-2-phenylethylcarbamoyl)heptanoic acid methyl ester (10.3 g, 91%) as an oil, which is used in the following step without purification.

Preparation 10

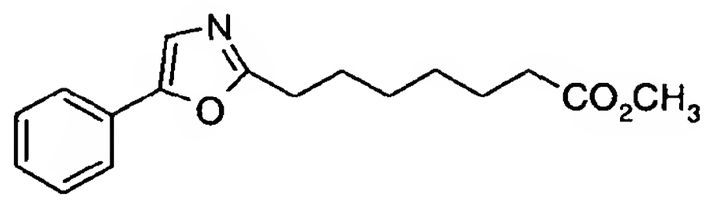
7-(2-Oxo-2-phenylethylcarbamoyl)heptanoic Acid Methyl Ester



Add Dess-Martin periodinane (16.5 g, 38.7 mmol) to a solution of 7-(2-oxo-2-phenylethylcarbamoyl)heptanoic acid methyl ester (Preparation 10, 10.2 g, 33.3 mmol) in methylene chloride (360 mL) at 0°C under nitrogen, stir and warm the mixture to room temperature for 4 hours. Filter the mixture through Celite, wash with ethyl acetate (3 x 100 mL) and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with hexane/ethyl acetate (60:40), to provide 7-(2-oxo-2-phenylethylcarbamoyl)heptanoic acid methyl ester (7.33 g, 72%) as a solid.

Preparation 11

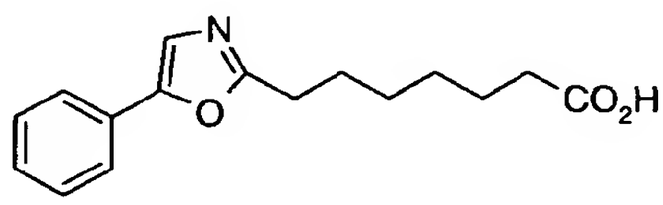
7-(5-Phenyloxazol-2-yl)heptanoic Acid Methyl Ester



Add a solution of 7-(2-oxo-2-phenylethylcarbamoyl)heptanoic acid methyl ester (Preparation 10, 7.05 g, 23.1 mmol) and carbon tetrabromide (11.3 g, 34.3 mmol) in methylene chloride over 40 minutes to a mixture of triphenylphosphine (9.0 g, 34.3 mmol) and DMAP (5.51 g, 45.1 mmol) in methylene chloride (500 mL) at room temperature under nitrogen. Stir the mixture for 30 minutes and add additional triphenylphosphine (2.6 g, 9.92 mmol) and carbon tetrabromide (3.35 g, 10.1 mmol). Stir the mixture for an additional 20 minutes, filter through Celite and wash with ethyl acetate (3 x 100 mL). Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (70:30), to provide 7-(5-phenyloxazol-2-yl)heptanoic acid methyl ester (2.75 g, 41%) as a solid.

Example 15

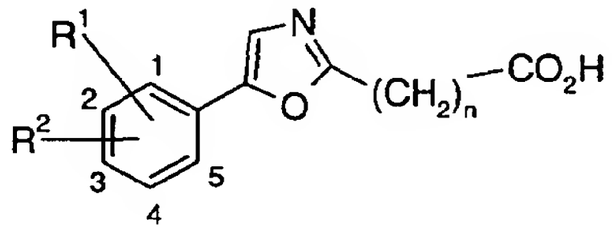
7-(5-Phenyloxazol-2-yl)heptanoic Acid



Add a solution of sodium hydroxide (1.80 g, 45.0 mmol) in water (30 mL) to a solution of 7-(5-phenyloxazol-2-yl)heptanoic acid methyl ester (Preparation 11, 9.0 g, 31.3 mmol) in methanol (30 mL) at room temperature and stir the mixture for 4 hours. Adjust the pH of the mixture to 2 with 1 N HCl and extract with ethyl acetate (500 mL). Wash the combined organic layers with water (3 x 100 mL), dry over sodium sulfate and

remove the solvent under reduced pressure. Crystallize the residue from ethyl acetate/hexanes to afford 7-(5-phenyloxazol-2-yl)heptanoic acid (7.3 g, 85%) as a solid: APCI mass spectrum *m/z* 272 $[C_{16}H_{19}NO_3 - H]^-$.

Prepare Examples 16-21, compounds of formula I(c) and Table 3 below, by the same process as in the preparation of Example 15.



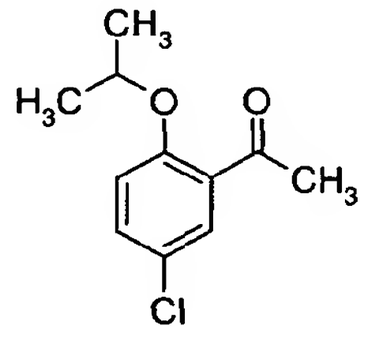
I(c)

Table 3: Compounds of formula I(c)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
16	OCH_3 (3)	H	6	302 $[C_{17}H_{21}NO_4 - H]^-$
17	OH (1)	Cl (4)	6	321 $[C_{16}H_{18}ClNO_4 - H]^-$
18	OCH_3 (1)	OCH_3 (4)	6	332$[C_{18}H_{23}NO_5 - H]^-$
19	OH (1)	H	4	260 $[C_{14}H_{15}NO_4 - H]^-$
20	OCH_3 (1)	H	6	302 $[C_{17}H_{21}NO_4 - H]^-$
21	OH (1)	H	6	288 $[C_{16}H_{19}NO_4 - H]^-$

Preparation 12

1-(5-Chloro-2-isopropoxyphenyl)ethanone

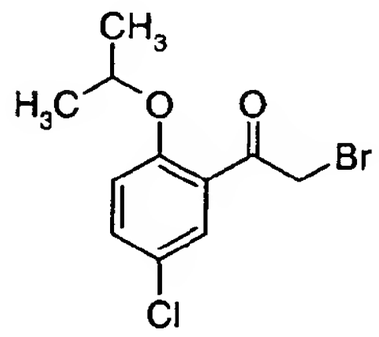


Add 2-Iodopropane (63.3 mL, 633 mmol) dropwise to a suspension of commercially available 1-(5-chloro-2-hydroxyphenyl)ethanone (90.0 g, 528 mmol) and potassium carbonate (109.46 g, 792mmol) in DMF (1000 mL) at room temperature under nitrogen and heat the mixture at 80°C for 22 hours. Cool and filter the mixture and

remove the solvent reduced pressure. Dilute the residue with ethyl acetate (1 L), wash with water (300 mL) and brine (200 mL), dry over sodium sulfate, and remove the solvent under reduced pressure to afford 1-(5-chloro-2-isopropoxyphenyl)ethanone (104.78 g, 93%) as an oil.

Preparation 13

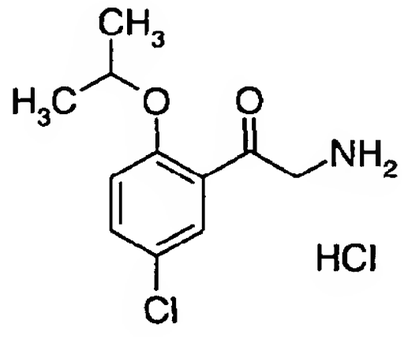
2-Bromo-1-(5-chloro-2-isopropoxyphenyl)ethanone



Add Copper(II) bromide (199 g, 891 mmol) portionwise to a solution of 1-(5-chloro-2-isopropoxyphenyl)ethanone (Preparation 12, 94.74 g, 446 mmol) in ethyl acetate (500 mL) and chloroform (500 mL) at room temperature under nitrogen. Heat the mixture at reflux for 4.5 hours. Cool the mixture and vacuum filter through a plug of Celite, washing with ethyl acetate (1 L). Remove the solvents under reduced pressure to provide 2-bromo-1-(5-chloro-2-isopropoxyphenyl)ethanone (128.46 g, 98%) as a solid.

Preparation 14

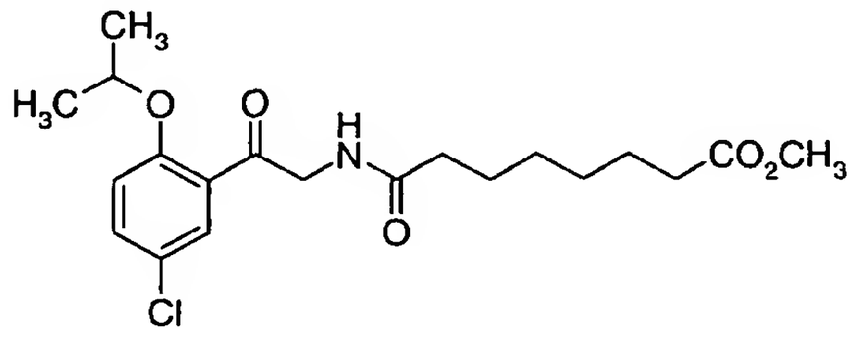
2-Amino-1-(5-chloro-2-isopropoxyphenyl)ethanone Hydrochloride



Add hexamethylenetetramine (36.14 g, 258 mmol) to a solution of 2-bromo-1-(5-chloro-2-isopropoxyphenyl)ethanone (Preparation 13, 75.17 g, 258 mmol) in chloroform (400 mL) at room temperature under nitrogen and stir for 2 days. Collect the solids by filtration, wash with diethyl ether, and dry overnight under reduced pressure. Suspend the solids in methanol (350 ml), cool to 0°C, and treat slowly with concentrated HCl (113 ml, 1365 mmol). Warm the mixture to room temperature and stir for 40 hours. Then heat the mixture to 55°C for an additional 4 hours. Remove the solids by filtration, and remove the filtrate solvent under reduced pressure to provide a solid. Triturate the solid with diethyl ether. Collect the resulting material by filtration to provide 2-amino-1-(5-chloro-2-isopropoxyphenyl)ethanone hydrochloride as a semi-solid, which is used in the next step without purification.

Preparation 15

7-[2-(5-Chloro-2-isopropoxyphenyl)-2-oxoethylcarbamoyl]heptanoic Acid Methyl Ester

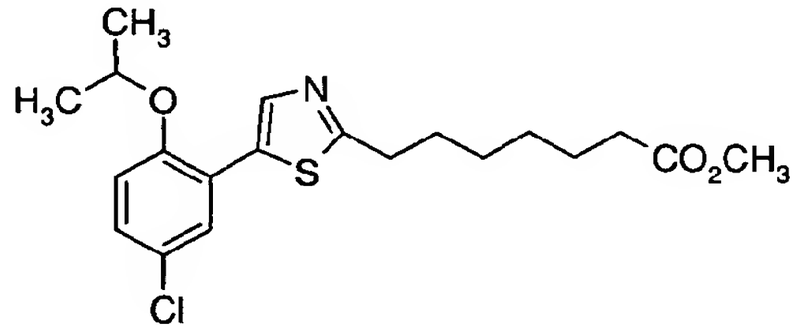


Add diisopropylethylamine (99 ml, 568 mmol) dropwise to a solution of EDC HCl (38.01 g, 198 mmol), HOBt (19.19 g, 142 mmol) and octanedioic acid monomethyl ester (53.44 g, 1.42 mmol) in methylene chloride (800 mL) at 0°C under nitrogen. Warm the mixture to room temperature and stir for 1 hour. Add 2-amino-1-(5-chloro-2-isopropoxyphenyl)ethanone hydrochloride (Preparation 14, 53.44 g, 142 mmol) to the mixture and stir for 18 hours. Remove the solvent under reduced pressure, dilute the residue in ethyl acetate (300 mL), wash with water (100 mL) and brine (100 mL), and dry over magnesium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate

(4:6 to 0:10), to afford 7-[2-(5-chloro-2-isopropoxyphenyl)-2-oxoethylcarbamoyl]-heptanoic acid methyl ester (23.87 g, 23% over three steps) as a solid.

Preparation 16

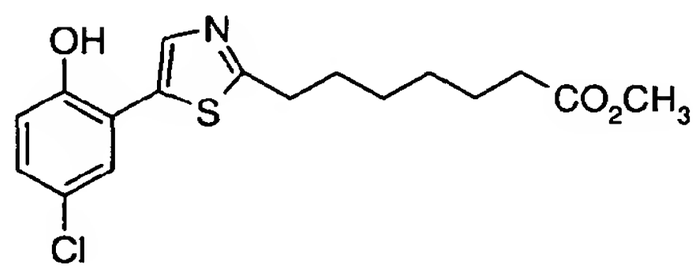
7-[5-(5-Chloro-2-isopropoxyphenyl)thiazol-2-yl]heptanoic Acid Methyl Ester



Add Lawesson's reagent (31.03 g, 77 mmol) to a solution of 7-[2-(5-chloro-2-isopropoxyphenyl)-2-oxoethylcarbamoyl]heptanoic acid methyl ester (Preparation 15, 21.80 g, 55 mmol) in THF (550 mL) at room temperature under nitrogen. Heat the mixture at reflux for 3 hours. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:3), to afford 7-[5-(5-chloro-2-isopropoxyphenyl)thiazol-2-yl]heptanoic acid methyl ester (9.96 g, 46%) as an orange oil.

Preparation 17

7-[5-(5-Chloro-2-hydroxyphenyl)thiazol-2-yl]heptanoic Acid Methyl Ester

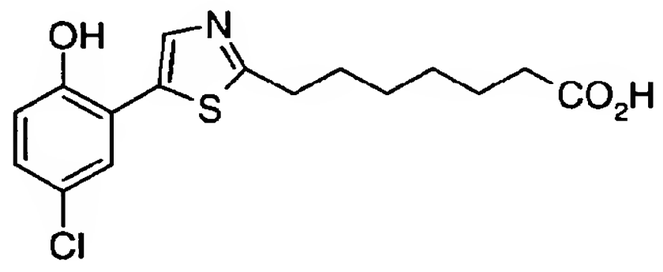


Add aluminum(III) chloride (6.67 g, 50 mmol) portionwise to a solution of 7-[5-(5-chloro-2-isopropoxyphenyl)thiazol-2-yl]heptanoic acid methyl ester (Preparation 16, 9.90 g, 25 mmol) in methylene chloride (300 mL) at 0°C under nitrogen. Slowly warm

the mixture to room temperature and stir for an additional 30 minutes. Cool the mixture to 0°C, treat with saturated aqueous sodium sulfate Na_2SO_4 (150 ml), and stir for 1 hour. Remove the solvent under reduced pressure, dilute the residue with ethyl acetate (300 mL), wash with water (100 mL) and brine (100 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:9 to 1:1), to afford 7-[5-(5-chloro-2-hydroxyphenyl)thiazol-2-yl]heptanoic acid methyl ester (5.67 g, 64%) as a solid.

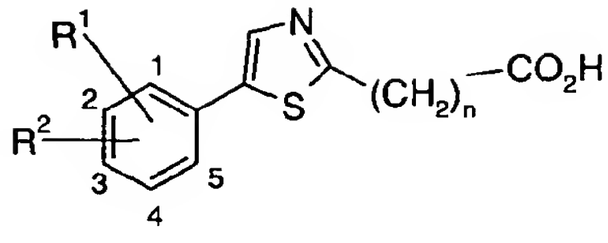
Example 22

7-[5-(5-Chloro-2-hydroxy-phenyl)-thiazol-2-yl]-heptanoic acid



Add a solution of sodium hydroxide (2.60 g, 65 mmol) in water (50 mL) to a solution of 7-[5-(5-chloro-2-hydroxyphenyl)thiazol-2-yl]heptanoic acid methyl ester (Preparation 17, 5.76 g, 16 mmol) in methanol (100 mL) at 0°C under nitrogen., warm the mixture to room temperature, and stir for a total of 1.5 hours. Remove the solvent under reduced pressure, dilute the residue with water (200 mL), cool to 0°C, and acidify to pH 1 with 1 N HCl. Collect the precipitate by filtration to afford 7-[5-(5-chloro-2-hydroxyphenyl)thiazol-2-yl]heptanoic acid (5.21g, 95%) as a solid: APCI mass spectrum *m/z* 338 $[C_{16}H_{18}ClNO_3S - H]^-$.

Prepare Examples 23 and 24, compounds of formula I(d) and Table 4 below, by the same process as in the preparation of Example 22.



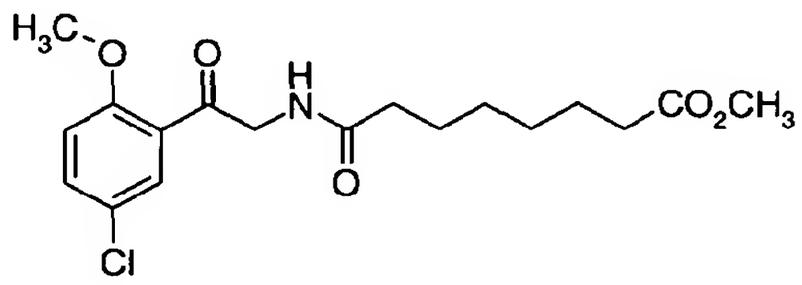
I(d)

Table 4: Compounds of formula I(d)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
23	OCH_3 (1)	H	6	320 $[C_{17}H_{21}NO_3S + H]^+$
24	OH (1)	H	6	304 $[C_{16}H_{19}NO_3S - H]^-$

Preparation 18

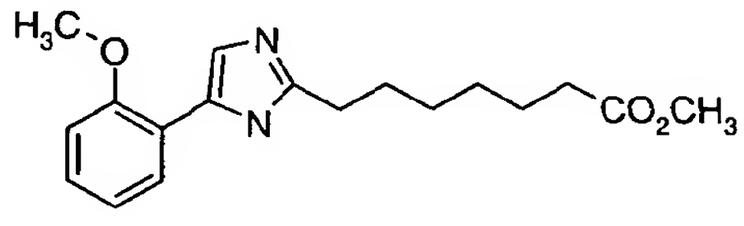
7-[2-(2-Methoxyphenyl)-2-oxoethylcarbamoyl]heptanoic Acid Methyl Ester



Add triethylamine (8.1 g, 79.9 mmol) dropwise to a solution of 2-amino-1-(2-methoxyphenyl)ethanone hydrochloride (13.6 g, 67.4 mmol) and octanedioic acid monomethyl ester (14.0 g, 74.2 mmol) in methylene chloride (600 mL) at 0°C under nitrogen, and then add EDC HCl (15.5 g, 81.0 mmol). Stir the mixture for 4 hours and warm to room temperature with stirring for an additional 18 hours. Dilute the mixture in ethyl acetate (1.2 L), wash sequentially with water (300 mL), 1 N HCl (300 mL), brine (300 mL), saturated sodium bicarbonate solution (300 mL) and brine (300 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure to afford 7-[2-(2-methoxyphenyl)-2-oxoethylcarbamoyl]heptanoic acid methyl ester (20.0 g, 88%) as a solid, which is used in the next step without further purification.

Preparation 19

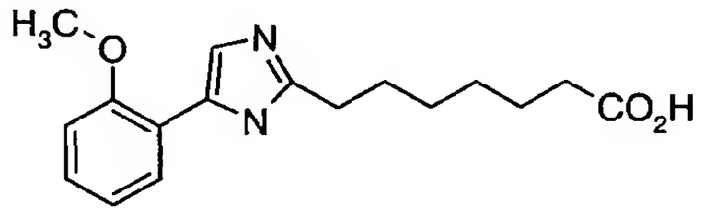
7-[5-(2-Methoxyphenyl)-1*H*-imidazol-2-yl]heptanoic Acid Methyl Ester



Heat a mixture of ammonium acetate (16.5 g, 214 mmol) and 7-[2-(2-methoxyphenyl)-2-oxoethylcarbamoyl]heptanoic acid methyl ester (Preparation 18, 14.2 g, 42.3 mmol) in acetic acid (300 mL) at reflux under nitrogen for 15 hours. Remove the solvent under reduced pressure. Dilute the residue in ethyl acetate (500 mL) and adjust to pH 8 with saturated aqueous sodium bicarbonate solution. Extract the aqueous layer with additional ethyl acetate (200 mL) and dry the combined organic extracts over sodium sulfate and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate, to afford 7-[5-(2-methoxyphenyl)-1*H*-imidazol-2-yl]heptanoic acid methyl ester (5.86 g, 44%) as a viscous oil: APCI mass spectrum *m/z* 317 $[C_{18}H_{24}N_2O_3 + H]^+$.

Example 25

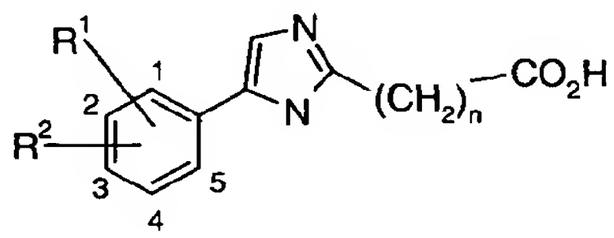
7-[5-(2-Methoxyphenyl)-1*H*-imidazol-2-yl]heptanoic Acid



Add a solution of sodium hydroxide (1.85 g, 46 mmol) in water (40 mL) to a solution of 7-[5-(2-methoxyphenyl)-1*H*-imidazol-2-yl]heptanoic acid methyl ester (Preparation 19, 5.84 g, 18.5 mmol) in methanol (30 mL) at room temperature under nitrogen and heat the mixture at 40°C for 4.5 hours. Cool the mixture and treat with 1 N HCl (46 mL) and heat at reflux for 30 minutes. Collect the precipitate, wash with water

(3 x 30 mL), and dry under reduced pressure for 12 hours. Triturate the solid with methylene chloride (50 mL) at reflux for 40 min and collect by filtration to provide 7-[5-(2-methoxyphenyl)-1*H*-imidazol-2-yl]heptanoic acid (4.27 g, 77%) as a solid. APCI mass spectrum *m/z* 301 $[C_{17}H_{22}N_2O_3 - H]^-$.

Prepare Examples 26-29, compounds of formula I(e) and Table 5 below, by the same process as in the preparation of Example 25.



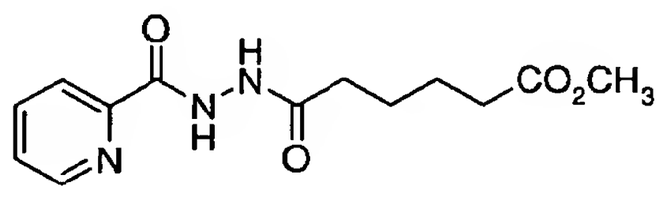
I(e)

Table 5: Compounds of formula I(e)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
26	H	H	6	271 $[C_{16}H_{20}N_2O_2 - H]^-$
27	H	OCH_3 (3)	6	301 $[C_{17}H_{22}N_2O_3 - H]^-$
28	H	OH (3)	6	287 $[C_{16}H_{20}N_2O_3 - H]^-$
29	OH (1)	H	6	287 $[C_{16}H_{20}N_2O_3 - H]^-$

Preparation 20

6-Oxo-6-[*N'*-(pyridine-2-carbonyl)hydrazino]hexanoic Acid Methyl Ester

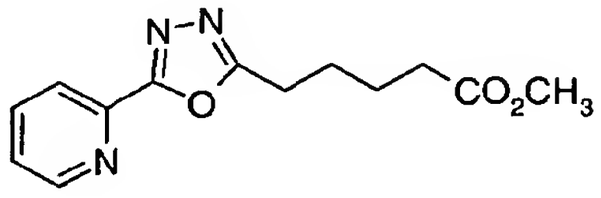


Stir a solution of commercially available 2-picolinylhydrazide (8.05 g, 58.8 mmol) and commercially available adipic acid monomethyl chloride (10.5 g, 58.8 mmol) in DMF (117 mL) at room temperature under nitrogen for 12 hours. Remove the solvent under reduced pressure. Triturate the residue with diethyl ether (300 mL), collect the

solids by filtration, dissolve in water (200 mL), and wash with ethyl acetate (200 mL). Adjust the pH to 8 with a saturated $NaHCO_3$ solution and extract with ethyl acetate (2 x 200 mL). Dry the combined organic extracts over sodium sulfate and remove the solvent under reduced pressure to provide 6-oxo-6-[*N*'-(pyridine-2-carbonyl)hydrazino]hexanoic acid methyl ester (3.85 g, 59%) as an oil.

Preparation 21

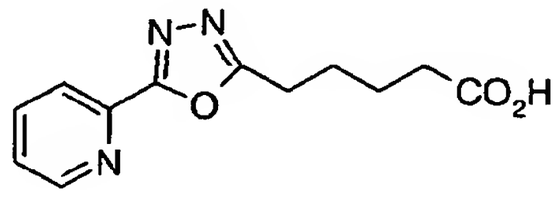
5-(5-Pyridin-2-yl[1,3,4]oxadiazol-2-yl)pentanoic Acid Methyl Ester



Add triethylamine (14.4 mL, 104 mmol) to a mixture of 6-oxo-6-[*N*'-(pyridine-2-carbonyl)hydrazino]hexanoic octanoic acid methyl ester (Preparation 20, 9.63 g, 34 mmol), carbon tetrachloride (26.6 g, 172 mmol) and triphenylphosphine (20.3 g, 78 mmol) in acetonitrile (35 mL) at room temperature under nitrogen and stir for 30 minutes. Remove the solids by filtration and then remove the filtrate solvent under reduced pressure. Dilute the residue with water (500 mL) and extract with ethyl acetate (3 x 500 mL). Wash the combined organic extracts with brine (200 mL), dry over sodium sulfate and remove the solvent under reduced pressure. Triturate the residue with ethyl acetate and collect the solids by filtration to afford 5-(5-pyridin-2-yl[1,3,4]oxadiazol-2-yl)pentanoic acid methyl ester (8.15 g, 91%) as a solid.

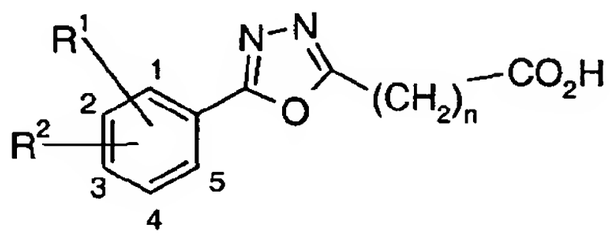
Example 30

5-(5-Pyridin-2-yl[1,3,4]oxadiazol-2-yl)pentanoic Acid



Add 2 N sodium hydroxide (20 mL) to a solution of 5-(5-pyridin-2-yl[1,3,4]oxadiazol-2-yl)pentanoic acid methyl ester (Preparation 21, 8.16 g, 31 mmol) in THF (60 mL) and methanol (20 mL) at room temperature under nitrogen and heat the mixture at reflux for 12 hours. Remove the solvent under reduced pressure, dilute the residue with water (500 mL), and wash with ethyl acetate (200 mL). Adjust the pH of the aqueous layer to pH 3 with concentrated HCl and extract with ethyl acetate (3 x 200 mL). Wash the combined organic extracts with brine (200 mL), dry over sodium sulfate, and remove the solvent under reduced pressure to afford 5-(5-pyridin-2-yl[1,3,4]oxadiazol-2-yl)pentanoic acid (2.05 g, 27%) as a yellow solid. APCI mass spectrum *m/z* 246 $[C_{12}H_{13}N_3O_3 + H]^+$.

Prepare Example 31, a compound of formula I(f) and Table 6 below, by the same process as in the preparation of Example 30.



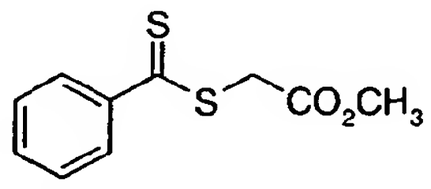
I(f)

Table 6: Compound of formula I(f)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
31	H	H	6	413 $[C_{16}H_{23}F_3N_2O_5S + H]^+$

Preparation 22

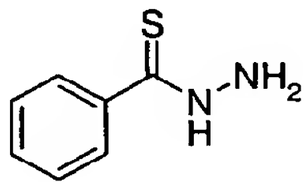
Thiobenzoylsulfanylacetic Acid Methyl Ester



Add a solution of commercially available thiobenzoylsulfanylacetic acid (5.5 g, 26.0 mmol) in methanol (100 mL) and to a solution of thionyl chloride (52 mL) at room temperature under nitrogen and heat the mixture at reflux for 12 hours. Remove the solvent under reduced pressure, dissolve the residue in ethyl acetate (200 mL), wash with saturated $NaHCO_3$ (200 mL) and brine (200 mL) solutions, and dry over sodium sulfate. Remove the solvent under reduced pressure to provide thiobenzoylsulfanylacetic acid methyl ester (5.7 g, 97%) as an oil.

Preparation 23

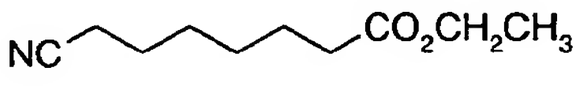
Thiobenzoic Acid Hydrazide



Add a solution of thiobenzoylsulfanylacetic acid methyl ester (Preparation 22, 1.9 g, 8.4 mmol) in ethanol (30 mL) to a solution of anhydrous hydrazine(1 mL) at room temperature under nitrogen and stir for 2 hours. Then add water (20 mL) and remove the solvent under reduced pressure. Dissolve the residue in ethyl acetate (300 mL), wash with water (200 mL) and brine (200 mL), and dry over magnesium sulfate. Remove the solvent under reduced pressure to provide thiobenzoic acid hydrazide (1.2 g, 94%) as a solid.

Preparation 24

7-Cyanoheptanoic Acid Ethyl Ester

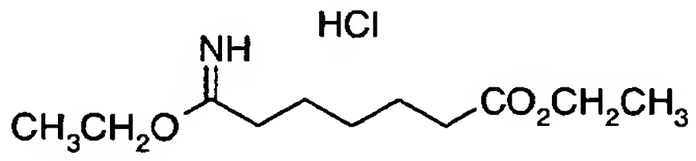


Add sodium cyanide (12.5 g, 255 mmol) and tetra-*n*-butylammonium iodide (10 g, 27.0 mmol) portionwise to a solution of commercially available 7-bromoheptanoic acid methyl ester (25 g, 105 mmol) in DMSO (300 mL) at room temperature under nitrogen

and heat the mixture at 50°C for 4 hours. Cool the mixture and dilute with water (200 mL) and extract with diethyl ether (2 x 200 mL). Dry the combined organic extracts over sodium sulfate and remove the solvent under reduced pressure to provide 7-cyanoheptanoic acid ethyl ester (18.2 g, 94%) as an amber oil.

Preparation 25

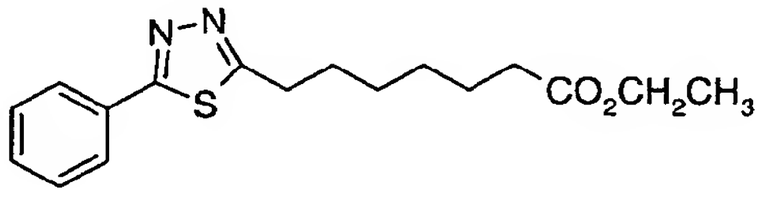
7-Ethoxycarbonimidoylheptanoic Acid Ethyl Ester Hydrochloride



Bubble hydrogen chloride gas into a solution of 7-cyanoheptanoic acid ethyl ester (Preparation 24, 3.7 g, 20.0 mmol) in ethanol (24 mL, 40 mmol) and diethyl ether (100 mL) at 0°C for 15 minutes. Remove the solvent under reduced pressure to provide 7-ethoxycarbonimidoylheptanoic acid ethyl ester (5.4 g, >99%) as an oil, which is used without further purification.

Preparation 26

7-(5-Phenyl[1,3,4]thiadiazol)heptanoic Acid Ethyl Ester

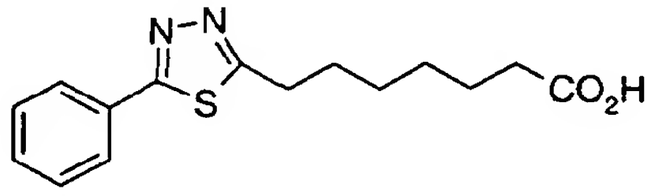


Heat a solution of thiobenzoic hydrazide (Preparation 23, 1.2 g, 7.90 mmol) and 7-ethoxycarbonimidoylheptanoic acid ethyl ester (Preparation 25, 2.9g, 11.0 mmol) in ethanol (35 mL) at reflux under nitrogen for 3 hours. Remove the solvent under reduced pressure. Dissolve the residue in ethyl acetate (200 mL), wash with water (200 mL) and brine (200 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with

hexane/ethyl acetate (4:1), to provide 7-(5-phenyl[1,3,4]thiadiazol)heptanoic acid ethyl ester (1.15 g, 45%) as a solid.

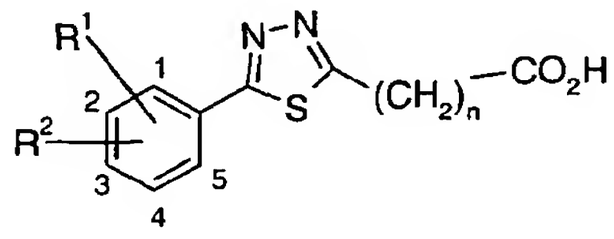
Example 32

7-(5-Phenyl[1,3,4]thiadiazol-2-yl)heptanoic Acid



Add a solution of potassium hydroxide (1.2 g 23 mmol) in water (50 mL) to a solution of 7-(5-phenyl-[1,3,4]thiadiazol)heptanoic acid ethyl ester (Preparation 26, 3.4 g, 11 mmol) in THF (30 mL) and methanol (30 mL) at room temperature under nitrogen and heat the mixture at reflux for 3 hours. Remove the solvent under reduced pressure, dilute the residue with water (200 mL) and wash with ethyl acetate (200 mL). Adjust the pH of the aqueous layer to 3 with concentrated HCl and extract with ethyl acetate (3 x 200 mL). Wash the combined organic extracts with brine (200 mL), dry over sodium sulfate and remove the solvent under reduced pressure to afford 7-(5-phenyl[1,3,4]thiadiazol-2-yl)heptanoic acid (2.9 g, 93%) as a solid. APCI mass spectrum *m/z* 289 $[C_{15}H_{18}N_2O_2S - H]^-$.

Prepare Examples 33-35, compounds of formula I(g) and Table 7 below, by the same process as in the preparation of Example 32.



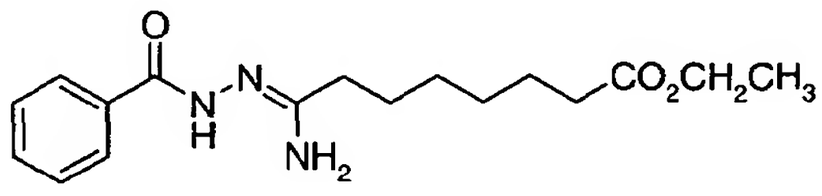
I(g)

Table 7: Compounds of formula I(g)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
33	OH (1)	OCH_3 (3)	6	335 $[C_{16}H_{20}N_2O_4S - H]^-$
34	OH (1)	H	6	305 $[C_{15}H_{18}N_2O_3S - H]^-$
35	OH (1)	Cl (4)	6	341 $[C_{15}H_{17}ClN_2O_3S + H]^+$

Preparation 27

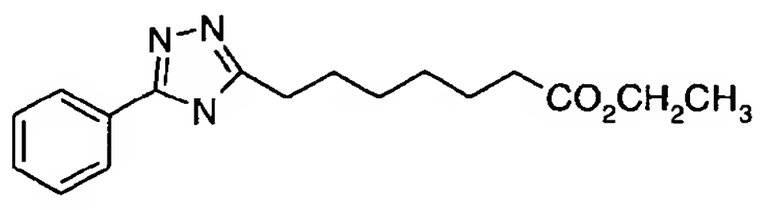
8-Amino-8-(benzoylhydrazono)octanoic Acid Ethyl Ester



Add triethylamine (5.6 mL, 40 mmol) to a solution of 7-ethoxycarbonimidoylheptanoic acid ethyl ester (11.0 g, 41 mmol) and benzoic acid hydrazide (5.5 g, 40 mmol) in ethanol (110 mL) at room temperature under nitrogen and stir the mixture for 12 hours. Remove the solvent under reduced pressure, dissolve the residue in ethyl acetate (200 mL), wash with saturated $NaHCO_3$ (200 mL) and brine (200 mL) solutions, and dry over sodium sulfate. Remove the solvent under reduced pressure to provide 8-amino-8-(benzoylhydrazono)octanoic acid ethyl ester (8.3 g, 64%) as a solid.

Preparation 28

7-(5-Phenyl-4*H*-[1,3,4]triazol-3-yl)heptanoic Acid Ethyl Ester

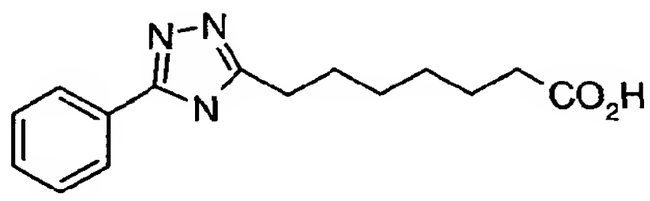


Heat a solution of 8-amino-8-(benzoylhydrazono)octanoic acid ethyl ester (Preparation 27, 4.2 g, 26 mmol) in o-xylene (400 mL) at reflux under nitrogen for 5

hours and then remove the solvent under reduced pressure. Dilute the residue with ethyl acetate (500 mL), wash with saturated $NaHCO_3$ (200 mL) and brine (200 mL) solutions and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with methanol/methylene chloride (1:9), to provide 7-(5-phenyl-4*H*-[1,3,4]triazol-3-yl)heptanoic acid ethyl ester (2.2 g, 58%) as an oil.

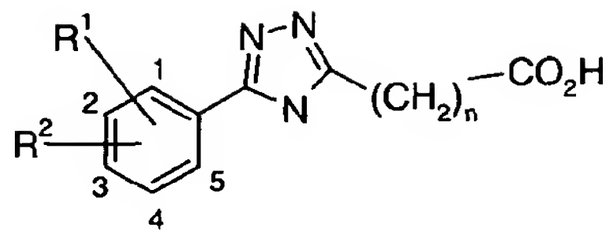
Example 36

7-(5-Phenyl-4*H*-[1,3,4]triazol-3-yl)-heptanoic acid



Add a solution of potassium hydroxide (1.8 g, 32 mmol) in water (70 mL) to a solution of 7-(5-phenyl-4*H*-[1,3,4]triazol-3-yl)heptanoic acid ethyl ester (Preparation 35, 4.9 g, 16 mmol) in THF (50 mL) and methanol (50 mL) at room temperature under nitrogen and heat the mixture at reflux for 3 hours. Remove the solvent under reduced pressure, dilute the residue with water (200 mL) and wash with ethyl acetate (200 mL). Adjust the pH of the aqueous layer to 3 with concentrated HCl and extract with ethyl acetate (3 x 200 mL). Wash the combined organic extracts with brine (200 mL), dry over sodium sulfate and remove the solvent under reduced pressure to afford 7-(5-phenyl-4*H*-[1,3,4]triazol-3-yl)heptanoic acid (4.4 g, 99%) as a solid. APCI mass spectrum *m/z* 273 $[C_{15}H_{19}N_3O_2]^-$.

Prepare Examples 37-39, compounds of formula I(h) and Table 8 below, by the same process as in the preparation of Example 36.



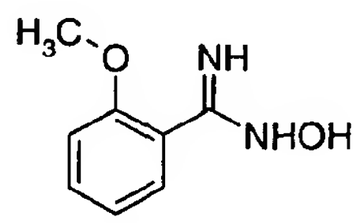
I(h)

Table 8: Compounds of formula I(h)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
37	OH (1)	OCH_3 (3)	6	319[$C_{16}H_{21}N_3O_4$ - H]$^-$
38	OH (1)	H	6	289[$C_{15}H_{19}N_3O_3$ - H]$^-$
39	OH (1)	Cl (4)	6	323[$C_{15}H_{18}ClN_3O_3$ - H]$^-$

Preparation 29

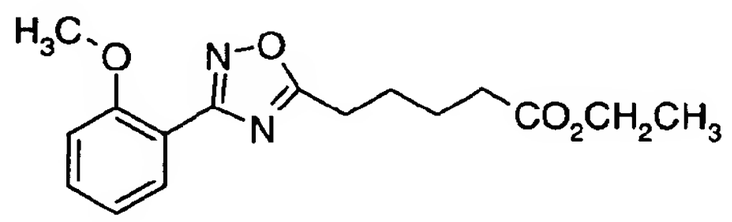
N-Hydroxy-2-methoxybenzamidine



Add potassium hydroxide (30.3 g, 225 mmol) to a solution of commercially available 2-methoxybenzonitrile (25.0 g, 187 mmol) and hydroxylamine hydrochloride (15.77 g, 225 mmol) in ethanol (500 mL) at room temperature under nitrogen and heat the mixture at reflux for 12 hours. Remove the solvent under reduced pressure, triturate the residue with ethyl acetate/hexanes (1:9, 300 mL) and collect by vacuum filtration to provide *N*-hydroxy-2-methoxybenzamidine (24.0 g, 91%) as a solid.

Preparation 30

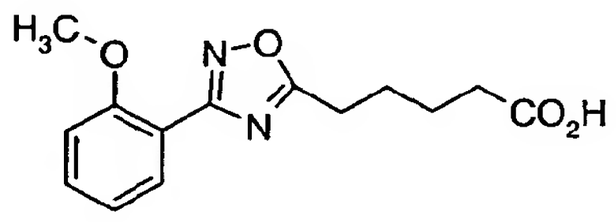
5-[3-(2-Methoxyphenyl)-[1,2,4]oxadiazol-5-yl]pentanoic Acid Methyl Ester



Add 5-chlorocarbonylpentanoic acid methyl ester (15.30 g, 86 mmol) to a solution of *N*-hydroxy-2-methoxybenzamidine (Preparation 29, 12.0 g, 71 mmol) in pyridine (40 mL) and under nitrogen at a rate to keep the mixture at a gentle reflux. Then, heat the mixture at reflux for 4 hours. Dilute the mixture with water (300 mL) and extract with methylene chloride (3 x 200 mL). Wash the combined organic extracts with brine (100 mL), dry over sodium sulfate and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:19), to afford 5-[3-(2-methoxyphenyl)-[1,2,4]oxadiazol-5-yl]pentanoic acid methyl ester (12.8 g, 55%) as a white solid.

Example 40

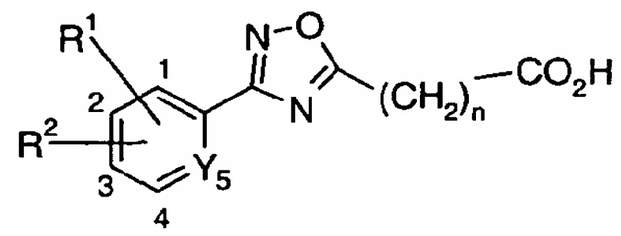
5-[3-(2-Methoxyphenyl)-[1,2,4]oxadiazol-5-yl]pentanoic Acid



Add 2 N sodium hydroxide (20 mL) to a solution of 5-[3-(2-methoxyphenyl)-[1,2,4]oxadiazol-5-yl]pentanoic acid ethyl ester (Preparation 30, 4.00 g, 13 mmol) in methanol (100 mL) at room temperature under nitrogen and stir the mixture for 3 hours. Remove the solvent under reduced pressure, dilute the residue with water (200 mL) and wash with diethyl ether (200 mL). Adjust the aqueous layer to pH 1 with 2 N HCl and

collect the solids by vacuum filtration to afford 5-[3-(2-methoxyphenyl)-[1,2,4]oxadiazol-5-yl]pentanoic acid (3.65 g, 99%) as a solid. APCI mass spectrum *m/z* 275 $[C_{14}H_{16}N_2O_4 - H]^-$.

Prepare Examples 41-44, compounds of formula I(i) and Table 9 below, by the same process as in the preparation of Example 40.



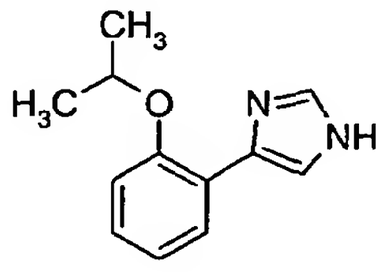
I(i)

Table 9: Compounds of formula I(i)

Example	R^1(position on ring)	R^2(position on ring)	Y	n	mass spectrum *m/z*
41	OH (1)	H	CH	4	261 $[C_{13}H_{14}N_2O_4 - H]^-$
42	CH_3 (2)	H	CH	7	301 $[C_{17}H_{22}N_2O_3 - H]^-$
43	CF_3 (3)	H	CH	7	355 $[C_{17}H_{19}F_3N_2O_3 - H]^-$
44	H	H	N	7	288$[C_{15}H_{19}N_3O_3 - H]^-$

Preparation 31

4-(2-Isopropoxy-phenyl)-1*H*-imidazole

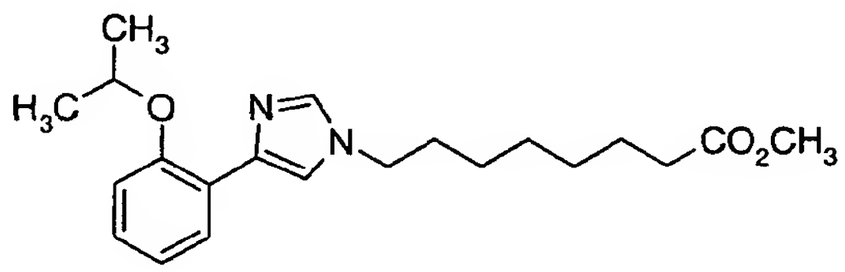


Add tetrakis(triphenylphosphine)palladium(0) (500 mg) to a degassed suspension of commercially available 4-bromo-1*H*-imidazole (5.0 g, 34 mmol) and commercially available 2-isopropoxyphenyl boronic acid (9.19 g, 51 mmol) in dioxane (250 mL) and 2 M sodium carbonate solution (10.81 g, 102 mmol) at room temperature under nitrogen

and heat the mixture at reflux for 21 hours. Remove the solvent under reduced pressure, dilute the residue with ethyl acetate (500 mL) and filter through a plug of Celite. Dry the filtrate over sodium sulfate, treat with silica gel (20 g) and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate, to afford crude 4-(2-isopropoxyphenyl)-1*H*-imidazole (5.01 g, 73%) as a white solid which was used without further purification in the next step.

Preparation 32

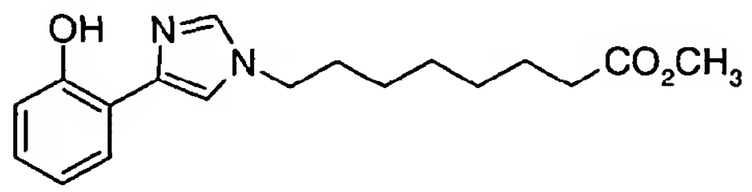
8-[4-(2-Isopropoxyphenyl)imidazol-1-yl]octanoic Acid Methyl Ester



Add sodium hydride (1.82 g, 38 mmol) to a suspension of 4-(2-isopropoxyphenyl)-1*H*-imidazole (Preparation 31, 5.01 g, 25 mmol) in THF (125 mL) at 0°C under nitrogen, and warm the mixture to room temperature and stir for 1 hour. Cool the mixture to 0°C and add 8-bromooctanoic acid methyl ester (5.98 g, 25 mmol) and tetra-*n*-butylammonium iodide (0.55 g, 1.5 mmol) and warm the mixture to room temperature to stir for 8 hours. Dilute the mixture with water (20 mL) and remove the solvent under reduced pressure. Dilute the residue with ethyl acetate (300 mL), wash with water (100 mL) and brine (100 mL), dry over sodium sulfate, and remove the solvent under reduced pressure to provide 8-[4-(2-isopropoxyphenyl)imidazol-1-yl]octanoic acid methyl ester (5.16 g, 57%) as an oil, which is used in the next step without further purification.

Preparation 33

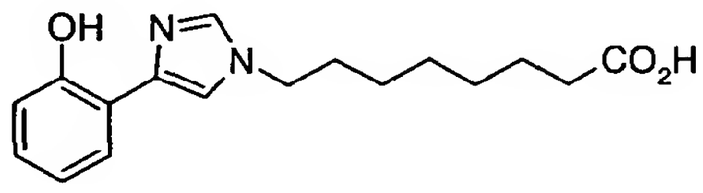
8-[4-(2-Hydroxyphenyl)imidazol-1-yl]octanoic Acid Methyl Ester



Add aluminum(III) chloride (3.84 g, 29 mmol) to a suspension of 8-[4-(2-isopropoxyphenyl)imidazol-1-yl]octanoic acid methyl ester (Preparation 32, 5.16 g, 14 mmol) in methylene chloride (150 mL) at 0°C under nitrogen. Warm the mixture to room temperature and stir for 6 hours. Dilute the mixture with saturated aqueous sodium sulfate (50 mL) and remove the solvent under reduced pressure. Dilute the residue with ethyl acetate (300 mL), wash with brine (100 mL), dry over sodium sulfate, and remove the solvent under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (2:8 to 3:7), to provide 8-[4-(2-hydroxyphenyl)imidazol-1-yl]octanoic acid methyl ester (2.63 g, 57%) as a solid.

Example 45

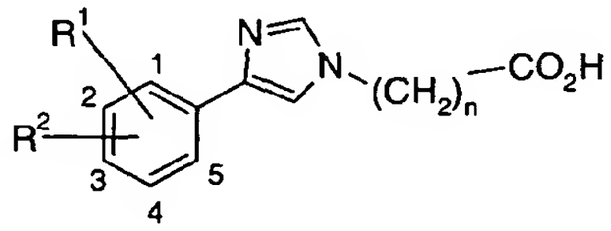
8-[4-(2-Hydroxyphenyl)imidazol-1-yl]octanoic Acid



Add sodium hydroxide (1.32 g, 33 mmol) in water (20 mL) to a suspension of 8-[4-(2-hydroxyphenyl)imidazol-1-yl]octanoic acid methyl ester (Preparation 33, 2.60 g, 8 mmol) in methanol (50 mL) at 0°C under nitrogen and warm the mixture to room temperature and stir for 8 hours. Remove the solvent under reduced pressure, dilute the residue with water (200 mL), cool to 0°C, and acidify to pH 1 with 1 N HCl. Collect the

precipitate to provide 8-[4-(2-hydroxyphenyl)imidazol-1-yl]octanoic acid (1.70 g, 68%) as a solid. APCI mass spectrum *m/z* 301 $[C_{17}H_{22}N_2O_3 - H]^-$.

Prepare Example 46, a compound of formula I(j) and Table 10 below, by the same process as in the preparation of Example 45.



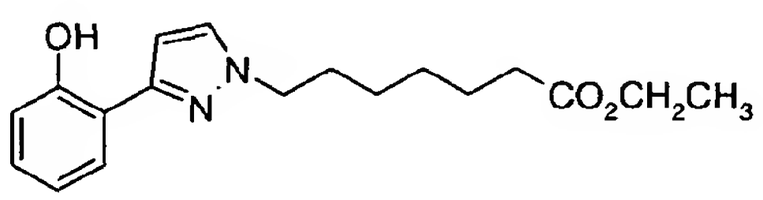
I(j)

Table 10: Compounds of formula I(j)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
46	H	H	7	285$[C_{17}H_{22}N_2O_2 - H]^-$

Preparation 34

7-[3-(2-Hydroxyphenyl)pyrazol-1-yl]heptanoic Acid Ethyl Ester

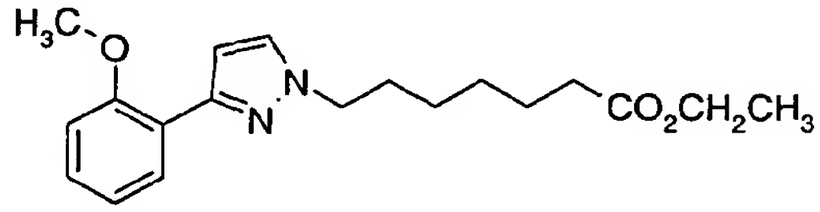


Add sodium hydride (1.50 g, 31 mmol, 60% suspension in mineral oil) to a suspension of commercially available 2-(1*H*-pyrazol-3-yl)phenol (5.0 g, 31 mmol) and 7-bromoheptanoic acid ethyl ester (7.4 g, 31 mmol) in DMF (75 mL) at room temperature under nitrogen and heat the mixture at 75°C for 16 hours. Remove the solvent under reduced pressure, dilute the residue with ethyl acetate (300 mL), wash with water (100 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with hexanes/ethyl

acetate (9:1), to provide 7-[3-(2-hydroxyphenyl)pyrazol-1-yl]heptanoic acid ethyl ester (4.73 g, 48%) as an oil.

Preparation 35

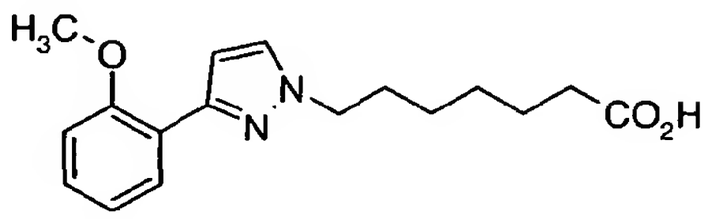
7-[3-(2-Methoxyphenyl)pyrazol-1-yl]heptanoic Acid Ethyl Ester



Add sodium hydride (900 mg, 18 mmol, 60% suspension in mineral oil) to a suspension of 7-[3-(2-hydroxyphenyl)pyrazol-1-yl]heptanoic acid ethyl ester (Preparation 34, 4.73 g, 15 mmol) and iodomethane (1.1 mL, 18 mmol) in THF (70 mL) at 0°C under nitrogen and warm the mixture to room temperature to stir for 12 hours. Remove the solvent under reduced pressure, dilute the residue with ethyl acetate (150 mL), wash with water (100 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with hexanes/ethyl acetate (9:1), to provide 7-[3-(2-Methoxyphenyl)pyrazol-1-yl]heptanoic acid ethyl ester (3.75 g, 76%) as a yellow oil.

Example 47

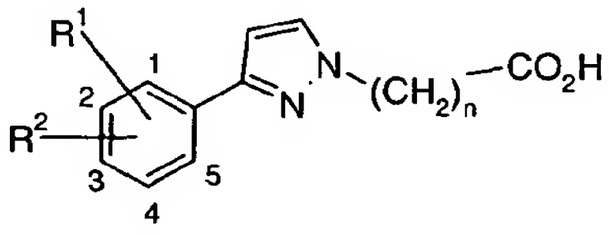
7-[3-(2-Methoxyphenyl)pyrazol-1-yl]heptanoic Acid



Add 2 N sodium hydroxide (20 mL) to a solution of 7-[3-(2-Methoxyphenyl)pyrazol-1-yl]heptanoic acid ethyl ester (Preparation 35, 3.75 g, 11.4 mmol) in methanol (40 mL) at room temperature under nitrogen and stir the mixture for 8

hours. Remove the solvent under reduced pressure, dilute the residue with water (100 mL), acidify to pH 3 with 1 N HCl, extract with ethyl acetate (200 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure to provide 7-[3-(2-methoxyphenyl)pyrazol-1-yl]heptanoic acid (3.06 g, 89%) as a solid. APCI mass spectrum *m/z* 303 $[C_{17}H_{22}N_2O_3 + H]^+$.

Prepare Examples 48-50, compounds of formula I(k) and Table 11 below, by the same process as in the preparation of Example 47.



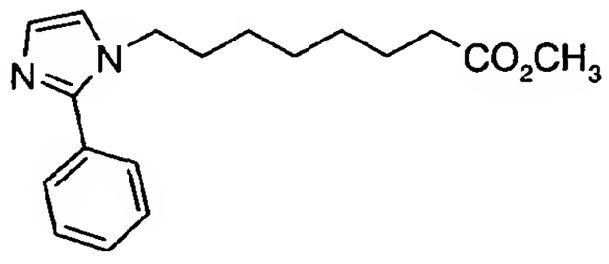
I(k)

Table 11: Compounds of formula I(k)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
48	OH (1)	H	6	289 $[C_{16}H_{20}N_2O_3 + H]^+$
49	OH (1)	Cl (4)	6	321$[C_{16}H_{19}ClN_2O_3 - H]^-$
50	OH (1)	Br (4)	6	366 $[C_{16}H_{19}BrN_2O_3 - H]^-$

Preparation 36

8-(2-Phenylimidazol-1-yl)octanoic Acid Methyl Ester

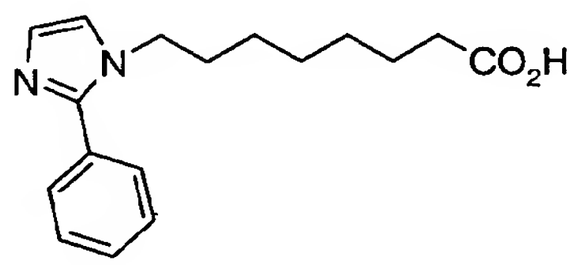


Add sodium hydride (1.3 g, 42 mmol) to a mixture of commercially available 2-phenyl-1*H*-imidazole (5.0 g, 35 mmol), 8-bromooctanoic acid methyl ester (8.22 g, 35 mmol), potassium carbonate (5.75 g, 42 mmol), and tetra-*n*-butylammonium iodide

(0.77g, 2mmol) in DMF (250 mL) at 0°C under nitrogen. Heat the mixture to 75°C and stir for 21 hours. Remove the solvent under reduced pressure, dissolve the residue in chloroform (200 mL), wash with water (100 mL) and brine (100 mL), and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with methanol/methylene chloride (1:9), to afford 8-(2-phenylimidazol-1-yl)octanoic acid methyl ester (4.90 g, 47%) as a brown residue.

Example 51

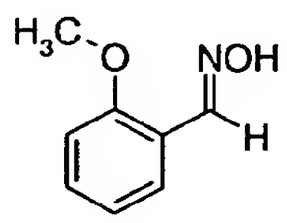
8-(2-Phenylimidazol-1-yl)octanoic Acid



Add sodium hydroxide (6.0 g, 150 mmol) in water (50 mL) to a suspension of 8-(2-phenylimidazol-1-yl)octanoic acid methyl ester (Preparation 36, 7.60 g, 25 mmol) in methanol (100 mL) at 0°C under nitrogen. Warm the mixture to room temperature and stir for a total of 8 hours. Remove the solvent under reduced pressure, dilute the residue with water (300 mL), cool to 0°C, and acidify to pH 1 with 1 N HCl. Collect the precipitate and triturate with hexanes to afford 8-(2-phenylimidazol-1-yl)octanoic acid (4.22 g, 52%) as a solid. APCI mass spectrum *m/z* 285 $[C_{17}H_{22}N_2O_2 - H]^-$.

Preparation 37

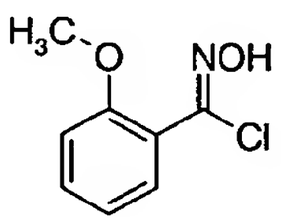
2-Methoxybenzaldehyde Oxime



Add sodium hydroxide (8.50 g, 220 mmol) in water (150 mL) to a solution of commercially available *o*-anisaldehyde (25.0 g, 180 mmol) and hydroxylamine hydrochloride (15.4 g, 220 mmol) in ethanol (150 mL) and water (150 mL) at room temperature and stir the mixture for 3 hours. Acidify the mixture to pH 6 with 1 N HCl solution and collect the solids by vacuum filtration to provide 2-methoxybenzaldehyde oxime (32.0 g, 99%) as a solid.

Preparation 38

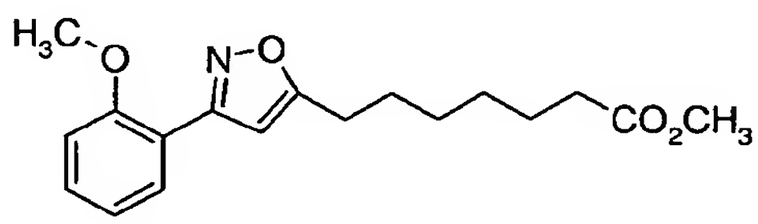
2-Methoxy-*N*-hydroxybenzenecarboxyimidoyl Chloride



Add *N*-Chlorosuccinimide (8.30 g, 65 mmol) portionwise to a solution of 2-methoxybenzaldehyde oxime (Preparation 37, 10.0 g, 65 mmol) in DMF (100 mL) at room temperature under nitrogen. Heat the mixture at 50°C for 5 hours. Pour the mixture into ice water (300 mL) collect the solids by vacuum filtration to provide 2-methoxy-*N*-hydroxybenzenecarboxyimidoyl chloride (9.80 g, 81%) as a solid.

Preparation 39

7-[3-(2-Methoxyphenyl)isoxazol-5-yl]heptanoic Acid Methyl Ester

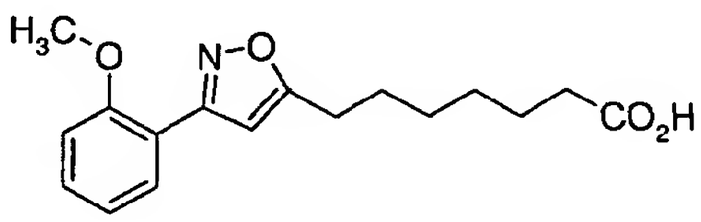


Add triethylamine (8.08 g, 80 mmol) to a solution of 2-methoxy-*N*-hydroxybenzenecarboxyimidoyl chloride (Preparation 38, 8.0 g, 40 mmol) and methyl 7-oxtynoate (10.50 g, 50 mmol) in THF (100 mL) at room temperature and stir the mixture

for 24 hours. Dilute the mixture with water (500 mL) and extract with ethyl acetate (3 x 200 mL). Wash the combined organic extracts with water (100 mL) and brine (100 mL) and dry over sodium sulfate. Remove the solvent under reduced pressure and purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:9), to afford 7-[3-(2-methoxyphenyl)isoxazol-5-yl]heptanoic acid methyl ester (7.80 g, 55%) as a solid.

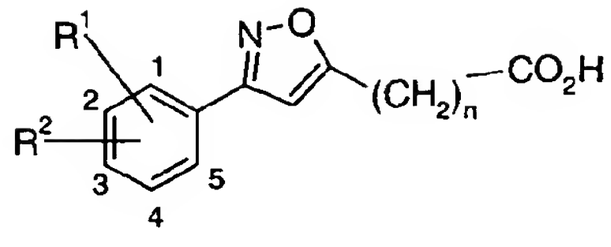
Example 52

7-[3-(2-Methoxyphenyl)isoxazol-5-yl]heptanoic Acid



Add 2 N sodium hydroxide (15 mL) to a solution of 7-[3-(2-methoxyphenyl)isoxazol-5-yl]heptanoic acid methyl ester (Preparation 39, 2.89 g, 8 mmol) in methanol (50 mL) at room temperature under nitrogen and stir for 3 hours. Remove the solvent under reduced pressure, dilute the residue with water (100 mL), and wash with methyl *tert*-butyl ether (100 mL). Acidify the mixture to pH 1 with 1 N HCl and extract with ethyl acetate (3 x 100 mL). Wash the combined organic extracts with water (100 mL) and brine (100), dry over sodium sulfate, and remove the solvent under reduced pressure to provide 7-[3-(2-methoxyphenyl)isoxazol-5-yl]heptanoic acid (2.41 g, 98%) as an off-white solid: APCI mass spectrum *m/z* 302 $[C_{17}H_{21}lNO_4 - H]^-$.

Prepare Examples 53-57, compounds of formula I(l) and Table 12 below, by the same process as in the preparation of Example 52.



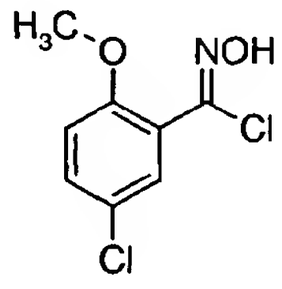
I(l)

Table 12: Compounds of formula I(l)

Example	R^1(position on ring)	R^2(position on ring)	n	mass spectrum *m/z*
53	OH (1)	H	4	260 $[C_{14}H_{15}NO_4 - H]^-$
54	OCH3 (1)	Cl (4)	4	309 $[C_{15}H_{16}ClNO_4 - H]^-$
55	OH (1)	Cl (4)	4	294 $[C_{14}H_{14}ClNO_4 - H]^-$
56	OH (1)	Cl (4)	6	322 $[C_{16}H_{18}ClNO_4 - H]^-$
57	OCH3 (1)	Cl (4)	6	337 $[C_{17}H_{20}ClNO_4 - H]^-$
58	OH (1)	H	6	288 $[C_{16}H_{19}NO_4 - H]^-$

Preparation 40

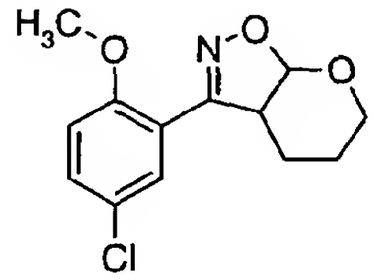
5-Chloro-2-methoxybenzenecarboxyimidoyl Chloride



Add *N*-Chlorosuccinimide (8.6 g, 65 mmol) portionwise to a solution of commercially available anisaldehyde oxime (10.0 g, 65 mmol) in DMF (250 mL) at room temperature under nitrogen and heat at 50°C for 6 hours. Pour the mixture into ice water (800 mL) and collect the solids by vacuum filtration to provide 5-chloro-2-methoxybenzenecarboxyimidoyl chloride (13.6 g, 92%) as a white solid.

Preparation 41

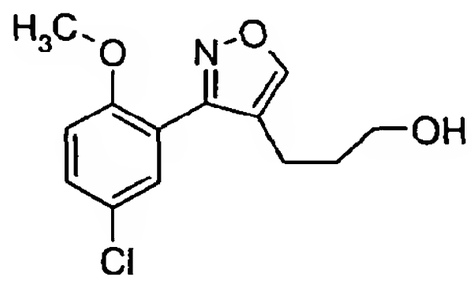
3-(5-Chloro-2-methoxyphenyl)-3a,5,6,7a-tetrahydro-4*H*-pyrano[3,2-d]isoxazole



Add triethylamine (10.1 mL, 100 mmol) to a solution of 5-chloro-2-methoxybenzenecarboxyimidoyl chloride (Preparation 40, 10.9 g, 50 mmol) and commercially available dihydropyran (4.2 g, 50 mmol) in THF (150 mL) at room temperature and stir the mixture for 48 hours. Dilute the mixture with water (500 mL) and extract with ethyl acetate (3 x 200 mL). Wash the combined organic extracts with brine (100 mL), dry over sodium sulfate and remove the solvents under reduced pressure to afford 3-(5-chloro-2-methoxyphenyl)-3a,5,6,7a-tetrahydro-4*H*-pyrano[3,2-d]isoxazole (12.9 g, >99%) as a tan oil that is used in the next step without purification.

Preparation 42

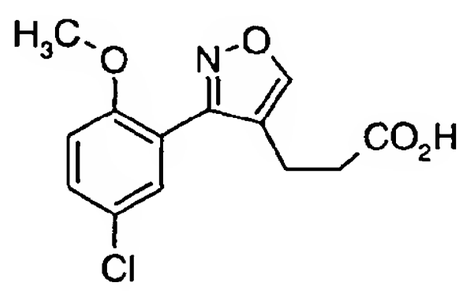
3-[3-(5-Chloro-2-methoxyphenyl)isoxazol-4-yl]propan-1-ol



Heat a solution of 3-(5-chloro-2-methoxyphenyl)-3a,5,6,7a-tetrahydro-4*H*-pyrano[3,2-d]isoxazole (Preparation 41, 12.0 g, 44 mmol) in 12 N HCl (200 mL) at 50°C for 24 hours and then dilute the mixture with water (300 mL) and extract with ethyl acetate (3 x 200 mL). Wash the combined organic extracts with brine (100 mL), dry over Na_2SO_4 and remove the solvents under reduced pressure. Purify the residue by flash column chromatography on silica gel, eluting with ethyl acetate/hexanes (1:1), to provide 3-[3-(5-chloro-2-methoxyphenyl)isoxazol-4-yl]propan-1-ol (8.0 g, 68%) as a white solid.

Example 59

3-[3-(5-Chloro-2-methoxyphenyl)isoxazol-5-yl]propionic Acid



Slowly add sodium perchlorate (2.0 g, 22 mmol) and bleach solution (1 mL) to a mixture of 3-[3-(5-chloro-2-methoxyphenyl)isoxazol-4-yl]propan-1-ol (Preparation 42, 3.0 g, 11 mmol), 2,2,6,6,-tetramethylpiperidinooxy (50 mg) in acetonitrile (30 mL), and saturated potassium phosphate solution (30 mL) at 35°C and stir the mixture for 12 hours. Adjust the pH of the mixture to pH 8 with 2 N NaOH solution and add saturated sodium sulfite solution (40 mL). Wash the mixture with *tert*-butyl methyl ether (2 x 20 mL), acidify to pH 1 with 1 N HCl and extract with ethyl acetate (3 x 100 mL). Wash the combined organic extracts with brine (100 mL), dry over Na_2SO_4 and remove the solvents under reduced pressure to provide 3-[3-(5-chloro-2-methoxyphenyl)isoxazol-5-yl]propionic acid (2.65 g, 85%) as a white solid: APCI mass spectrum *m/z* 280 $[C_{13}H_{12}ClNO_4 - H]^-$.

Preparation 43

5-[2-(2-methoxyphenyl)-2-oxo-ethylcarbamoyl]-pentanoic acid methyl ester

Add sodium azide (2.14 g, 32.92 mmol) to a solution of 2-bromo-2'-methoxyacetophenone (5.01 g, 21.87 mmol) in 75 ml of DMSO. Stir the mixture at ambient temperature for 18 hours and dilute it with 250 ml of water. Extract the mixture with ether (3X). Dry the combined organic layers with $MgSO_4$. Filter off the drying agent and concentrate in vacuo to afford 3.54 g of 2-azido-1-(2-methoxyphenyl)-ethanone.

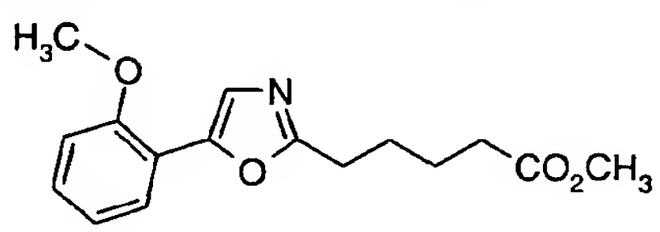
Dissolve 2-azido-1-(2-methoxy-phenyl)-ethanone (3.54 g, 18.5 mmol) in 1328 ml of MeOH and 9 ml of concentrated HCl. Add 943 mg of 10% Pd/C and expose the

reaction mixture to 60 psi of H_2 for 5 hours at ambient temperature. Filter the catalyst off through a pad of celite and concentrate the filtrate in vacuo to afford 3.74 g of crude 2-amino-1-(2-methoxyphenyl)-ethanone as the hydrochloride salt.

Dissolve 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.57 g, 18.62 mmol), 4-(dimethylamino)pryidine (463.8 mg, 3.79 mmol) and adipic acid monomethyl ester (2.97 g, 18.55 mmol) in 100 mL of CH_2Cl_2 and allow it to stir at room temperature for 45 minutes. Add crude 2-amino-1-(2-methoxy-phenyl)-ethanone hydrochloride (3.74 g, 18.55 mmol) and triethylamine (3.75 g, 37.1 mmol) to the reaction mixture and allow it to stir at ambient temperature for 22 hours. Dilute the reaction with 200 mL of CH_2Cl_2 and wash it with 1 N HCl (2X), saturated aqueous $NaHCO_3$ (2X) and brine (1X). Dry the organic layer with $MgSO_4$. Filter the drying agent and concentrate in vacuo to afford 4.57 g of the titled product (80%): mass spectrum: m/z = 308.1 (M+H).

Preparation 44

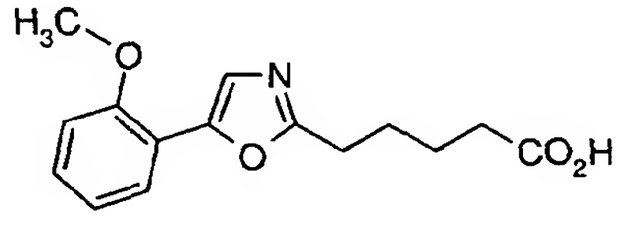
5-[5-(2-methoxyphenyl)-oxazol-2-yl)-pentanoic acid methyl ester



Dissolve 5-[2-(2-methoxy-phenyl)-2-oxo-ethylcarbamoyl]-pentanoic acid methyl ester (Preparation 43, 4.57 g, 14.87 mmol) and 4-(dimethylamino)pryidine (3.56 g, 29.14 mmol) in 150 mL CH_2Cl_2 and cool the reaction mixture in an ice bath. Add triphenylphosphinedibromide (12.32 g, 1.96 mmol) to the reaction portionwise over 15 minutes. Raise the reaction to ambient temperature and allow it to stir for 12 hours. Wash the reaction with water and brine (2X). Dry the organic layers with $MgSO_4$. Filter off the drying agent and concentrate in vacuo to afford a crude residue. Purify the residue using silica gel chromatography eluting with hexanes/ethyl acetate mixtures to afford 2.47 g of the titled product (57%): mass spectrum: m/z = 290.1 (M+H).

Example 60

5-[5-(2-methoxy-phenyl)-oxazol-2-yl]-pentanoic acid



Dissolve 5-[5-(2-methoxy-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester (Preparation 44, 2.47 g, 8.54 mmol) in 40 mL of dioxane and add a solution of LiOH (1.0344 g, 43.19 mmol) in 20 mL of water to the solution. Allow the reaction to stir at ambient temperature for 21 hours. Acidify the reaction with 5N HCl and concentrate the reaction mixture in vacuo to remove the dioxane. Extract the aqueous residue with EtOAc (3X). Dry the combined organic layers with $MgSO_4$. Filter off the drying agent and concentrate in vacuo to afford a crude residue. Recrystallize the residue in EtOAc/hexanes to afford 1.7692 g of the titled product (75%): mass spectrum: m/z = 276.1 (M+H).

Preparation 45

5-[2-(5-Chloro-2-methoxy-phenyl)-2-oxo-ethylcarbamoyl]-pentanoic acid methyl ester

Dissolve 5'-chloro-2'-hydroxyacetophenone (15.3594 g, 90.03 mmol) in 100 mL of anhydrous acetonitrile in a pressure vessel. Add K_2CO_3 (13.7541 g, 99.52 mmol) and MeI (25.56 mL, 180.06 mmol) to the vessel. Seal the vessel and heat the reaction mixture to 85°C for 18 hours. Cool the reaction and concentrate it in vacuo. Partition the residue between Et_2O and H_2O. Wash the organic layers with 2N NaOH (2X). Dry the combined organic layers with $MgSO_4$. Filter off the drying agent and concentrate in vacuo to afford 13.15 g of 1-(5-chloro-2-methoxy-phenyl)-ethanone (79%).

Suspend $CuBr_2$ (29.44 g, 131.81 mmol) in 150 mL EtOAc and heat it to reflux. Dissolve 1-(5-chloro-2-methoxy-phenyl)-ethanone (13.15 g, 71.23 mmol) in 100 mL of $CHCl_3$ and add it dropwise to the reaction. After 4 hours, filter the reaction to remove the solids. Concentrate the filtrate in vacuo and dissolve the residue in EtOAc. Wash the organic layer with saturated aqueous $NaHCO_3$ and water. Dry the organic layer with

$MgSO_4$. Filter off the drying agent and concentrate in vacuo to afford 17.07 g of 2-bromo-1-(5-chloro-2-methoxy-phenyl)-ethanone.

Dissolve 2-bromo-1-(5-chloro-2-methoxy-phenyl)-ethanone (17.07 g, 64.78 mmol) in 150 mL of $CHCl_3$ and add hexamethylenetetramine (9.09 g, 64.84 mmol) to the reaction mixture. Allow the reaction to stir at ambient temperature for 23 hours. Collect the solids via filtration and wash the solids with Et_2O. Slurry the solid in 100 mL of MeOH and add 50 mL of concentrated HCl to it dropwise. Heat the reaction to reflux and allow it to stir for 23 hours. Cool the reaction to ambient temperature and filter off the solids. Slurry the filtrate in MeOH and again collect the solids via filtration. Concentrate the filtrate to afford 10.99 g of 2-amino-1-(5-chloro-2-methoxy-phenyl)-ethanone hydrochloride.

Dissolve 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (8.0362 g, 41.92 mmol), 4-(dimethylamino)pryidine (1.0525g, 8.62 mmol) and adipic acid monomethyl ester (6.71 g, 41.90 mmol) in 100 mL of CH_2Cl_2 and allow it to stir at room temperature for 45 minutes. Add crude 2-amino-1-(5-chloro-2-methoxy-phenyl)-ethanone hydrochloride (10.99 g, 46.55 mmol) and triethylamine (9.42 g, 93.1 mmol) to the reaction mixture and allow it to stir at ambient temperature for 21 hours. Dilute the reaction with 200 mL of CH_2Cl_2 and wash it with 1 N HCl (2X), saturated aqueous $NaHCO_3$ (2X) and brine (1X). Dry the organic layer with $MgSO_4$. Filter off the drying agent and concentrate in vacuo to afford 9.39 g of the crude titled product: mass spectrum: m/z = 342.1 (M+H).

Preparation 46

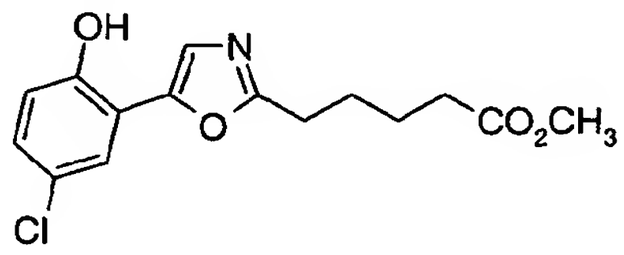
5-[5-(5-chloro-2-methoxy-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester

Dissolve 5-[2-(5-Chloro-2-methoxy-phenyl)-2-oxo-ethylcarbamoyl]-pentanoic acid methyl ester (Preparation 45, 9.39 g, 27.47 mmol) and 4-(dimethylamino)pyridine (6.54 g, 53.53 mmol) in 250 mL of CH_2Cl_2 and cool the reaction mixture in an ice bath. Add triphenylphosphinedibromide (22.54 g, 53.40 mmol) to the reaction portionwise over 15 minutes. Raise the reaction to ambient temperature and allow it to stir for 17 hours. Wash the reaction with water (1X) and brine (2X). Dry the organic layers with $MgSO_4$.

Filter off the drying agent and concentrate in vacuo to afford a crude residue. Purify the residue using silica gel chromotagraphy eluting with hexanes/ethyl acetate mixtures to afford 4.38 g of the titled product (49%): mass spectrum: m/z = 324.1 (M+H).

Preparation 47

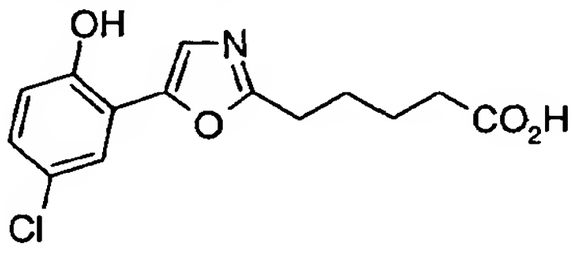
5-[5-(5-Chloro-2-hydroxy-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester



Dissolve 5-[5-(5-chloro-2-methoxy-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester (Preparation 46, 4.174 g, 12.89 mmol) in 50 mL of CH_2Cl_2 and cool the solution to –78°C. Add boron tribromide (48.9 mL of a 1M solution in CH_2Cl_2) dropwise to the reaction and allow it to warm to ambient temperature and allow it to stir for 27 hours. Cool the reaction to –78°C and quench it by adding 100 mL of MeOH dropwise to the reaction mixture. Allow the reaction to warm to ambient temperature and stir for 19 hours. Concentrate the reaction mixture in vacuo. Dissolve the residue in CH_2Cl_2 and wash it with saturated aqueous $NaHCO_3$ and brine. Dry the organic layer with $MgSO_4$. Filter off the drying agent and concentrate in vacuo to afford a crude residue. Purify the residue using silica gel chromotagraphy eluting with hexanes/ethyl acetate mixtures to afford 3.26 g of the titled product (82%): mass spectrum: m/z = 310.09 (M+H).

Example 61

5-[5-(5-Chloro-2-hydroxy-phenyl)-oxazol-2-yl]-pentanoic acid

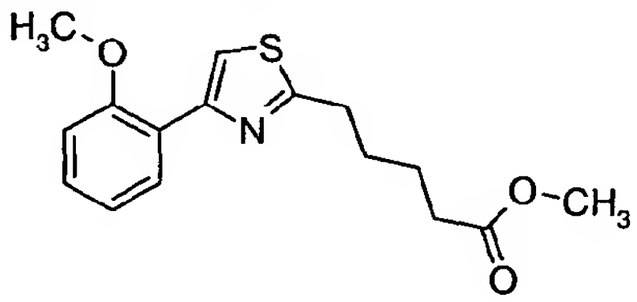


Dissolve 5-[5-(5-chloro-2-hydroxy-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester (Preparation 47, 3.26 g, 10.52 mmol) in 50 mL of dioxane and add a solution of LiOH (1.2671 g, 50.91 mmol) in 25 mL of water to it. Allow the reaction to stir at

ambient temperature for 18 hours. Acidify the reaction with 5N HCl and concentrate the reaction mixture in vacuo to remove the dioxane. Extract the aqueous residue with EtOAc (3X). Dry the combined organic layers with $MgSO_4$. Filter off the drying agent and concentrate in vacuo to afford a crude residue. Triturate the residue in cold EtOAc. Collect the product via filtration to afford 1.8837 g of the titled product (60%): mass spectrum: m/z = 296.1 (M+H).

Preparation 48

5-[4-(2-methoxy-phenyl)-thiazol-2-yl]-pentanoic acid methyl ester



Bubble gaseous ammonia through a gas dispersion tube through a rapidly stirred 0°C solution of methyl adipoyl chloride (17.0 mL, 100.0 mmol) in dioxane (200 mL, anhydrous) for 30 minutes. Allow to warm to room temperature. After 1 hour, filter out solid ammonium chloride and concentrate mother liquor to get 20 grams of a white solid. Add 20% i-PrOH/$CHCl_3$ to material, dry over $MgSO_4$ and concentrate to afford 5-carbamoyl-pentanoic acid methyl ester (15.09 g, 95%) as a white solid.

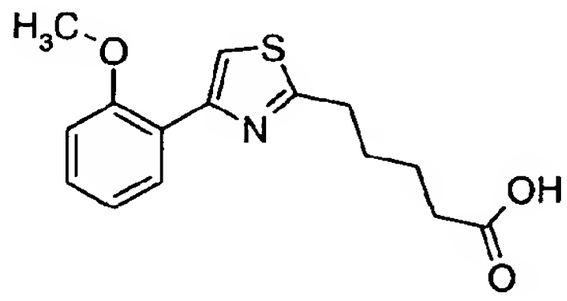
Add THF (200 mL, anhydrous) to a sealed vessel containing 5-carbamoyl-pentanoic acid methyl ester (11.94 g, 75.0 mmol) and phosphorous pentasulfide (16.67 g, 37.5 mmol). Flush vessel with N_2, seal, and sonicate for 75 minutes. Break up solids and stir sealed under N_2 at room temperature for 50 hours. Concentrate, triturate with boiling $CHCl_3$ and filter hot (x3). Concentrate combined mother liquors to get 14.5 g yellow residue. Purify the residue by flash chromatography on silica gel eluting with 0-60% EtOAc/hexanes to afford 5-thiocarbamoyl-pentanoic acid methyl ester (7.72 g, 59%) as a white solid.

Add THF (125 mL, anhydrous) to a sealed vessel containing 5-thiocarbamoyl-pentanoic acid methyl ester (7.25 g, 41.4 mmol) and 2-bromo-2'-methoxyacetophenone (9.48 g, 41.4 mmol). Flush vessel with N_2, seal, and heat at 80°C overnight. Cool to

romm temperature, add EtOAc, wash with saturated aqueous $NaHCO_3$ solution, brine, and backextract from each aqueous layer with EtOAc. Dry combined organic layers over $MgSO_4$ and concentrate to get 18 grams of purple residue. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 0-20% EtOAc/hexanes to afford the title compound (9.7 g, 77%) as a yellow oil. TLC (30% EtOAc/hexanes) R_f = 0.38. MS (IS) 306 $(M+1)^+$.

Example 62

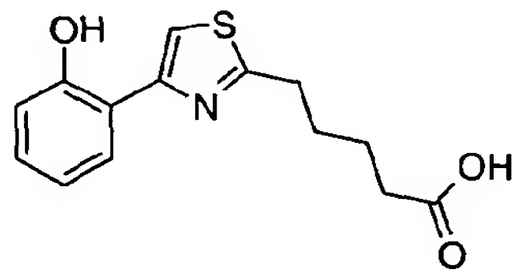
5-[4-(2-methoxy-phenyl)-thiazol-2-yl]-pentanoic acid



Add a solution of $LiOH \cdot H_2O$ (2.62 g, 62.5 mmol) in water (60 mL) to a rapidly stirred solution of 5-[4-(2-methoxy-phenyl)-thiazol-2-yl]-pentanoic acid methyl ester (Preparation 48, 3.82 g, 12.5 mmol) in dioxane (120 mL), stir at room temperature. After 1 hour, acidify to pH 1 with 5N HCl solution and concentrate to remove the majority of the dioxane. Partition residue between 20% i-PrOH/$CHCl_3$ and 1N HCl solution, separate layers. Backextract from aqueous layer with 20% i-PrOH/$CHCl_3$ and dry combined organic layers over $MgSO_4$, and concentrate to get 3 grams of a pink oil. Recrystallize from EtOAc to afford the title compound (2.52 g, 69%) as a white solid. MS (IS) 292 $(M+1)^+$.

Example 63

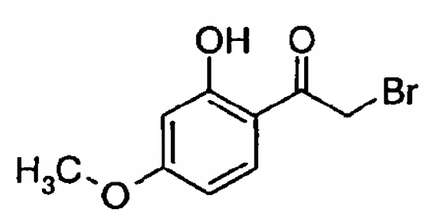
5-[4-(2-hydroxy-phenyl)-thiazol-2-yl]-pentanoic acid



Dissolve 5-[4-(2-methoxy-phenyl)-thiazol-2-yl]-pentanoic acid methyl ester (Preparation 48, 3.20 g, 10.5 mmol) in acetic acid (50 mL, glacial), add HBr (50 mL, 48% aqueous solution) and heat to reflux under N_2 for 6 hours. Add additional HBr (20 mL, 48% aqueous solution) and heat at reflux under N_2 overnight. Adjust to pH 4 with 5N NaOH solution, extract with EtOAc (x2), dry over $MgSO_4$ and concentrate to get 2.64 grams of a light brown solid. Recrystallize from EtOAc/hexanes to afford the title compound (2.14 g, 74%) as a light tan solid. MS (IS) 278 $(M+1)^+$.

Preparation 49

2-bromo-1-(2-hydroxy-4-methoxy-phenyl)-ethanone

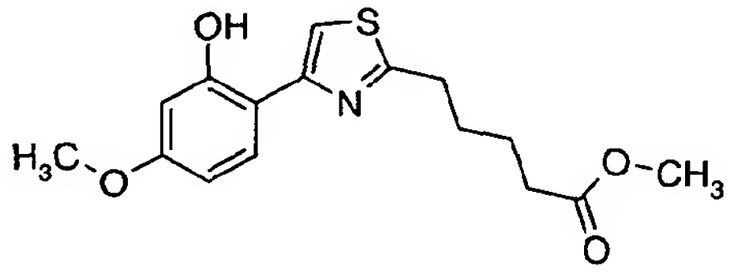


Heat a suspension of copper (II) bromide (16.79 g, 75.2 mmol) in EtOAc (40 mL) to reflux under N_2. Add a solution of 2'-hydroxy-4'-methoxyacetophenone (7.48 g, 45.0 mmol) in $CHCl_3$ (40 mL) to the suspension dropwise over 3 minutes. Attach a drying tube to the top of the condenser and reflux for 6 hours. Cool to room temperature and stir under N_2 overnight. Filter mixture and rinse filter cake with EtOAc and $CHCl_3$, concentrate mother liquor to get 12.75 grams of a green oily solid. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 0-20%

EtOAc/hexanes to afford the crude (approx. 75% pure) title compound (8.5 g, 77%) as a yellow oil.

Preparation 50

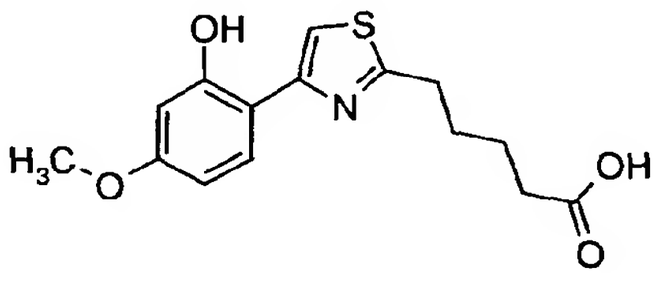
5-[4-(2-hydroxy-4-methoxy-phenyl)-thiazol-2-yl]-pentanoic acid methyl ester



Add THF (50 mL, anhydrous) to a roundbottom flask containing 5-thiocarbamoyl-pentanoic acid methyl ester (2.63 g, 15.0 mmol) and 2-bromo-1-(2-hydroxy-4-methoxy-phenyl)-ethanone (Preparation 49, 4.90 g, 15.0 mmol, 75% pure). Heat to reflux under N_2 overnight. Cool to room temperature, add EtOAc, wash with saturated $NaHCO_3$ solution, brine, and backextract from each aqueous layer with EtOAc. Dry combined organic layers over $MgSO_4$ and concentrate to get 8 grams of a yellow solid. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 0-20% EtOAc/hexanes followed by flash chromatography on silica gel eluting with $CHCl_3$ to afford the title compound (2.69 g, 56%) as a white solid. MS (IS) 322 $(M+1)^+$.

Example 64

5-[4-(2-hydroxy-4-methoxy-phenyl)-thiazol-2-yl]-pentanoic acid

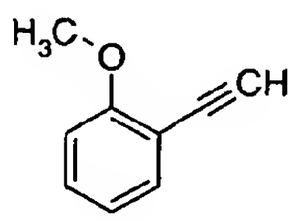


Add a solution of $LiOH \cdot H_2O$ (1.76 g, 41.9 mmol) in water (25 mL) to a rapidly stirred solution of 5-[4-(2-hydroxy-4-methoxy-phenyl)-thiazol-2-yl]-pentanoic acid methyl ester (Preparation 50, 2.69 g, 8.4 mmol) in dioxane (50 mL), stir at room

temperature. After 1 hour, acidify to pH 1 with 5N HCl solution and cool under N_2 in a refrigerator. Filter out solids and rinse with ice cold water. Dry solids in a vacuum oven overnight to afford the title compound (2.50 g, 96%) as a light tan solid. MS (IS) 308 $(M+1)^+$.

Preparation 51

1-ethynyl-2-methoxy-benzene

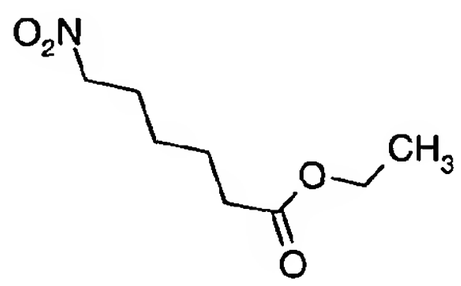


Add 2-iodo-anisole (17.55 g, 75.0 mmol), trimethylsilyl acetylene (15.9 mL, 112.5 mmol), copper (I) iodide (0.29 g, 1.5 mmol), and THF (225 mL, anhydrous) to a dry round bottom flask. Add diisopropylamine (22.1 mL, 157.5 mmol) and dichlorobis(triphenylphosphine) palladium (II) (1.58 g, 2.3 mmol) and stir the mixture at room temperature under N_2. After 2.5 hours, quench reaction with water and extract with EtOAc (x2). Wash combined organic layers with brine, dry over $MgSO_4$ and concentrate to get 20.8 grams of a black oil. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 0-5% EtOAc/hexanes to afford 2-methoxy-phenylethynyl)-trimethylsilane (13.2 g, 86%) as an orange oil.

Add a solution of potassium hydroxide (3.66 g, 65.2 mmol) in water (30 mL) dropwise over 30 minutes to a stirred solution of (2-methoxy-phenylethynyl)-trimethylsilane (13.2 g, 64.6 mmol) in methanol (275 mL) and stir at room temperature for 1.5 hours. Concentrate, add brine to residue, and extract with EtOAc. Dry organic layer over $MgSO_4$ and concentrate to get 10.5 grams of a black oil. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 0-5% EtOAc/hexanes to afford the title compound (7.6 g, 89%) as an orange oil.

Preparation 52

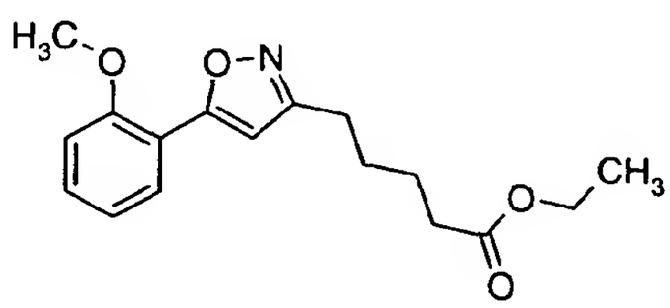
6-nitro-hexanoic acid ethyl ester



Add silver nitrite (23.1 g, 150 mmol) to a stirred solution of ethyl 6-bromo-hexanoate (17.7 mL, 100 mmol) in diethyl ether (125 mL, anhydrous) and heat to reflux under N_2 overnight. Filter through a pad of Celite® and rinse pad with diethyl ether, concentrate to get 21 grams of a yellow oil. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 0-20% EtOAc/hexanes to afford the title compound (14.0 g, 74%) as a clear oil.

Preparation 53

5-[5-(2-methoxy-phenyl)-isoxazol-3-yl]-pentanoic acid ethyl ester



Add 1,4-phenylenediisocyanate (14.5 g, 90.8 mmol) to a stirred solution of 1-ethynyl-2-methoxy-benzene (Preparation 51, 4.0 g, 30.3 mmol) and 6-nitro-hexanoic acid ethyl ester (Preparation 52, 8.6 g, 45.4 mmol) in toluene (300 mL, anhydrous) and stir under N_2. Add triethylamine (12.7 mL, 90.8 mmol) and heat to reflux under N_2. After 2.5 hours, filter mixture through a pad of Celite® and rinse with toluene. Concentrate to get 9 grams of a orange oil. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 0-20% EtOAc/hexanes to afford the title compound (14.0 g, 74%) as a clear oil.

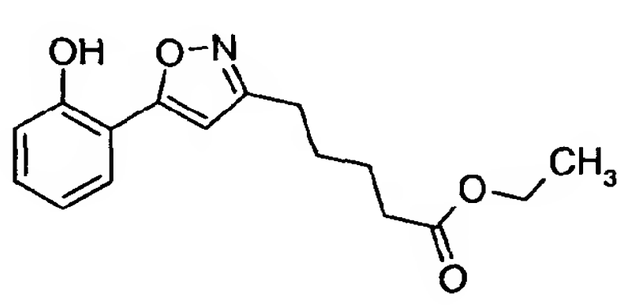
Example 65

5-[5-(2-methoxy-phenyl)-isoxazol-3-yl]-pentanoic acid

Add a solution of $LiOH \cdot H_2O$ (1.83 g, 43.5 mmol) in water (30 mL) to a rapidly stirred solution of 5-[5-(2-methoxy-phenyl)-isoxazol-3-yl]-pentanoic acid ethyl ester (Preparation 53, 2.64 g, 8.7 mmol) in dioxane (60 mL) and stir overnight at room temperature. After 1 hour, acidify to pH 1 with 5N HCl solution and concentrate to remove the majority of the dioxane. Partition residue between 20% i-PrOH/$CHCl_3$ and 1N HCl solution and separate layers. Backextract from aqueous layer with 20% i-PrOH/$CHCl_3$ and dry combined organic layers over $MgSO_4$, and concentrate to get 2.5 grams of a yellow oil. Recrystallize from EtOAc/hexanes to afford the title compound (1.96 g, 82%) as a white solid. MS (IS) 276 $(M+1)^+$.

Preparation 54

5-[5-(2-hydroxy-phenyl)-isoxazol-3-yl]-pentanoic acid ethyl ester

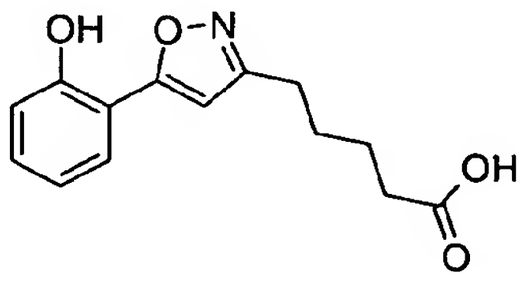


Add boron tribromide (43 mL, 43 mmol, 1.0 M solution in CH_2Cl_2) dropwise over 30 minutes to a stirred 0°C solution of 5-[5-(2-methoxy-phenyl)-isoxazol-3-yl]-pentanoic acid ethyl ester (Preparation 53, 5.20 g, 17.1 mmol) in CH_2Cl_2 (45 mL). Allow to warm to room temperature overnight. Add boron tribromide (17 mL, 17 mmol, 1.0 M solution in CH_2Cl_2) and stir at room temperature under N_2. After 4 hours, add boron tribromide

(17 mL, 17 mmol, 1.0 M solution in CH_2Cl_2) and stir at room temperature under N_2. After 2 hours, quench via dropwise addition of ethanol (50 mL, absolute). Concentrate, dissolve residue in $CHCl_3$, wash with saturated $NaHCO_3$ solution (x2), dry over $MgSO_4$ and concentrate to get 4.7 g of a tan solid. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 3-20% EtOAc/hexanes to afford the title compound (3.96 g, 80%) as a white solid. MS (IS) 290 $(M+1)^+$.

Example 66

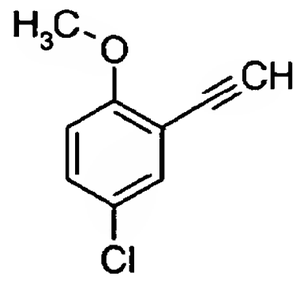
5-[5-(2-hydroxy-phenyl)-isoxazol-3-yl]-pentanoic acid



Add a solution of $LiOH \cdot H_2O$ (2.87 g, 68.4 mmol) in water (60 mL) to a rapidly stirred solution of 5-[5-(2-hydroxy-phenyl)-isoxazol-3-yl]-pentanoic acid ethyl ester (Preparation 54, 3.96 g, 13.7 mmol) in dioxane (120 mL) and stir at room temperature overnight. After 1 hour, acidify to pH 1 with 5N HCl solution and concentrate to remove the majority of the dioxane. Add water to residue and place in refrigerator overnight. Filter out solids, wash with water, dry in a 50°C vacuum oven for 6 hours to afford the title compound (3.11 g, 87%) as a white solid. MS (IS) 262 $(M+1)^+$.

Preparation 55

4-chloro-2-ethynyl-1-methoxy-benzene



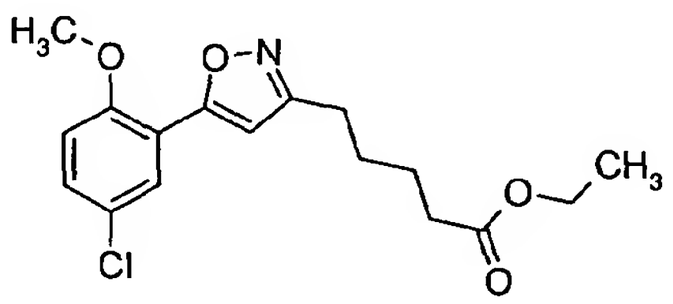
Add 4-chloro-2-iodo-anisole (10.9 mL, 75.0 mmol), trimethylsilyl acetylene (15.9 mL, 112.5 mmol), copper (I) iodide (0.29 g, 1.5 mmol), and THF (225 mL, anhydrous) to

a dry round bottom flask. Add diisopropylamine (22.1 mL, 157.5 mmol) and dichlorobis(triphenylphosphine) palladium (II) (1.58 g, 2.3 mmol) and stir the mixture at room temperature under N_2 overnight. Quench reaction with water and extract with EtOAc (x2). Wash combined organic layers with brine, dry over $MgSO_4$ and concentrate to get 24 g of a black oil. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 0-3% EtOAc/hexanes to afford (5-chloro-2-methoxy-phenylethynyl)-trimethylsilane (13.7 g, 76%) as a tan solid.

Add a solution of potassium hydroxide (3.28 g, 58.5 mmol) in water (30 mL) dropwise over 25 minutes to a stirred solution of (5-chloro-2-methoxy-phenylethynyl)-trimethylsilane (13.7 g, 57.4 mmol) in methanol (275 mL) and stir at room temperature for 2 hours. Concentrate, add brine to residue, and extract with EtOAc (x2). Dry organic layer over $MgSO_4$ and concentrate to get 13 g of a black oil. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 0-5% EtOAc/hexanes to afford the title compound (8.98 g, 94%) as a tan solid.

Preparation 56

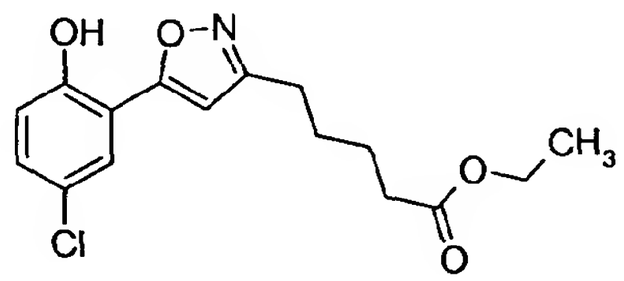
5-[5-(5-chloro-2-methoxy-phenyl)-isoxazol-3-yl]-pentanoic acid ethyl ester



Add 1,4-phenylenediisocyanate (8.41 g, 52.5 mmol) to a stirred solution of 4-chloro-2-ethynyl-1-methoxy-benzene (4.0 g, 30.3 mmol) and 6-nitro-hexanoic acid ethyl ester (8.6 g, 45.4 mmol) in toluene (300 mL, anhydrous) and stir at room temperature under N_2. Add triethylamine (7.3 mL, 52.5 mmol) and heat to reflux under N_2 overnight. Filter mixture through a pad of Celite® and rinse with toluene. Concentrate to get 6.6 g of a orange oil. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 0-40% EtOAc/hexanes to afford the title compound (4.51 g, 76%) as a yellow solid. MS (IS) 338 $(M+1)^+$.

Preparation 57

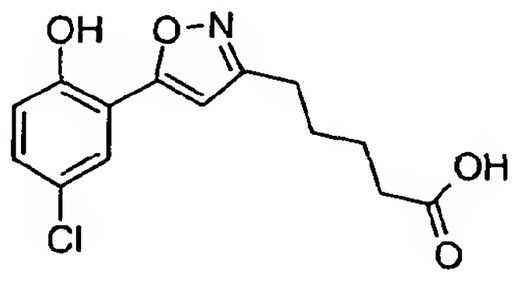
5-[5-(5-chloro-2-hydroxy-phenyl)-isoxazol-3-yl]-pentanoic acid ethyl ester



Add boron tribromide (39 mL, 39 mmol, 1.0 M solution in CH_2Cl_2) dropwise to a stirred -78°C solution of 5-[5-(5-chloro-2-methoxy-phenyl)-isoxazol-3-yl]-pentanoic acid ethyl ester (Preparation 56, 4.39 g, 13 mmol) in CH_2Cl_2 (40 mL). Allow to warm to room temperature. After 2 hours, cool to -78°C and add boron tribromide (13 mL, 13 mmol, 1.0 M solution in CH_2Cl_2) dropwise and allow to warm to room temperature overnight. Quench via dropwise addition of ethanol (60 mL, absolute). Concentrate, dissolve residue in $CHCl_3$, wash with saturated $NaHCO_3$ solution (x2), dry over $MgSO_4$ and concentrate to get 3.7 g of a tan solid. Adsorb on SiO_2 and purify the residue by flash chromatography on silica gel eluting with 0-60% EtOAc/hexanes to afford the title compound (3.3 g, 78%) as a light yellow solid. MS (IS) 324 $(M+1)^+$.

Example 67

5-[5-(5-chloro-2-hydroxy-phenyl)-isoxazol-3-yl]-pentanoic acid

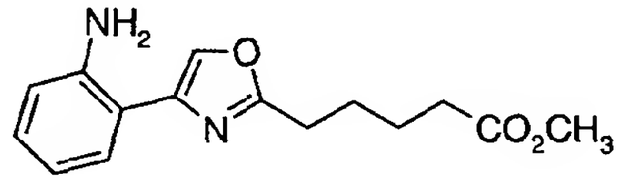


Add a solution of $LiOH \cdot H_2O$ (2.14 g, 51.0 mmol) in water (30 mL) to a rapidly stirred solution of 5-[5-(5-chloro-2-hydroxy-phenyl)-isoxazol-3-yl]-pentanoic acid ethyl ester (Preparation 57, 3.30 g, 10.2 mmol) in dioxane (60 mL), stir at room temperature overnight. After 1 hour, acidify to pH 1 with 5N HCl solution and place in refrigerator.

Filter out solids and rinse with water to afford the title compound (2.73 g, 91%) as a white solid. MS (IS) 296 $(M+1)^+$.

Preparation 58

5-[4-(2-amino-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester



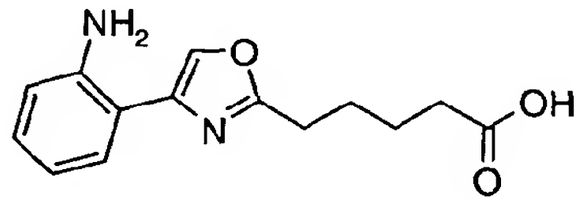
Dissolve methyl adipoyl chloride (27 mL, 159 mmol) in dioxane (300 mL) and place the vessel in a room temperature water bath. Carefully bubble in ammonia gas (excess) and allow the mixture to stir for 1-2 hours. Filter the mixture to remove solids. Suspend solids in $CHCl_3$ and filter again. Concentrate the combined filtrates and dry in vacuo to give 24.87 g (98 %) of 5-carbamoyl-pentanoic acid methyl ester as a white solid.

Combine 2-bromo-2'-nitroacetophenone (9.6 g, 39.3 mmol) with 5-carbamoyl-pentanoic acid methyl ester (12.0 g, 75.5 mmol) and heat the neat mixture in a sealed vessel at 120-140°C for about 6 hours. Cool the mixture and add methanol and allow the mixture to stir overnight at room temperature. Concentrate the mixture and partition the residue between aq $NaHCO_3$ and EtOAc. Dry the combined extracts over Na_2SO_4 and concentrate. Initial chromatography over silica gel (CH_2Cl_2) followed by a second chromatography over silica gel (Hex/EtOAc) allowed for recovery of 5-[4-(2-nitro-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester (4.65 g, 39 %) as a light oil. MS(ES): $(M+1)^+$ 305.1, 306.3 m/z.

Combine 5-[4-(2-nitro-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester (2.5 g, 8.2 mmol) with 5% Pd/C (300 mg) and Pd/black (50 mg) in THF and react with hydrogen (init. 39 psi) in a Parr® apparatus. When reduction is complete, filter the mixture through Celite® and concentrate the filtrate. Chromatograph the residue over silica gel ($MeOH/CH_2Cl_2$) to allow for recovery of 2.05 g (91%) of 5-[4-(2-amino-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester as an oil. MS(ES): $(M+1)^+$ 275.1, 276.2 m/z.

Example 68

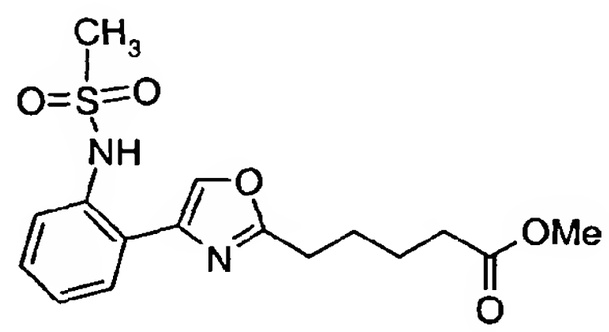
5-[4-(2-amino-phenyl)-oxazol-2-yl]-pentanoic acid



Combine 5-[4-(2-amino-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester (Preparation 58, 2.5 g, 9.1 mmol) with THF (3 mL), EtOH (3 mL) and 1N NaOH (15 mL) and stir until hydrolysis is complete. Concentrate the mixture, dilute the residue with water and adjust the pH to 2.5-3.5 with aq HCl. Extract the mixture with EtOAc and dry the extracts over Na_2SO_4 before concentrating. Chromatograph the residue over silica gel (EtOAc) to allow for recovery of 5-[4-(2-amino-phenyl)-oxazol-2-yl]-pentanoic acid (2.03 g, 86 %) as a light tan solid. MS(ES): $(M+1)^+$ 261.1 m/z.

Preparation 59

5-[4-(2-methanesulfonylamino-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester

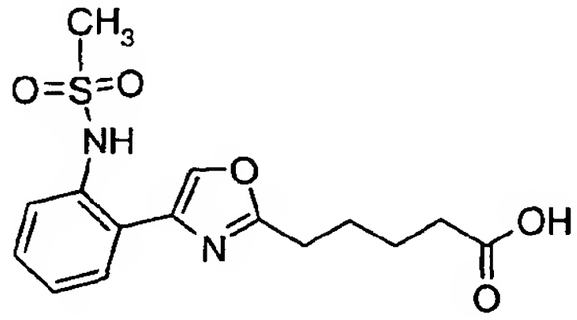


Dissolve 5-[4-(2-amino-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester (Preparation 58, 2.18 g, 7.96 mmol) in THF (50 mL) and add pyridine (1.20 mL, 14.8 mmol). Add methanesulfonyl chloride (excess) and allow the mixture to stir at room temperature until reaction is complete. Concentrate the mixture and quench the residue with ice/aq $NaHCO_3$ and extract with EtOAc. Dry the combined extracts over Na_2SO_4 and concentrate. Chromatograph the residue over silica gel (EtOAc/CH_2Cl_2) to allow for isolation of 5-[4-(2-methanesulfonylamino-phenyl)-oxazol-2-yl]-pentanoic acid methyl

ester as an oil which crystallizes upon standing (2.8 g, 100%). MS(ES): $(M+1)^+$ 353.2, 354.3 m/z.

Example 69

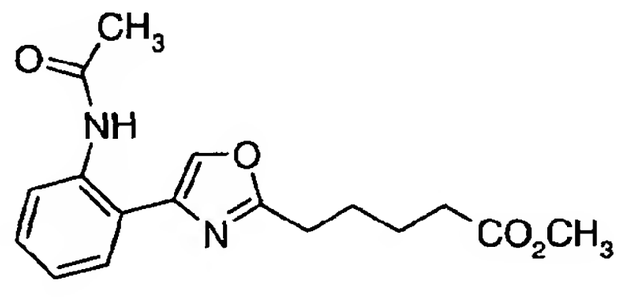
5-[4-(2-methanesulfonylamino-phenyl)-oxazol-2-yl]-pentanoic acid



Combine 5-[4-(2-methanesulfonylamino-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester (Preparation 59, 2.75 g, 7.8 mmol) with THF (3 mL), EtOH (3 mL) and 1N NaOH (20 mL) and stir at room temperature until hydrolysis is complete. Concentrate the mixture and dilute the residue with water and adjust to pH 3.0–3.5 with aq HCl. Extract the mixture with EtOAc and dry the extracts over Na_2SO_4 before concentrating. Chromatograph the residue over silica gel (EtOAc) to allow for recovery of 5-[4-(2-methanesulfonylamino-phenyl)-oxazol-2-yl]-pentanoic acid (2.16 g, 82 %) as a light solid. MS(ES): (M+1)+ 339.2, 340.3.

Preparation 60

5-[4-(2-acetylamino-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester

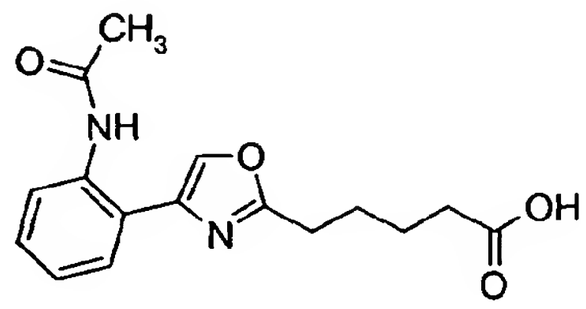


Dissolve 5-[4-(2-amino-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester (Preparation 58, 4.05 g, 14.8 mmol) and triethylamine (2.26 mL, 16.2 mmol) in THF (40

mL) and stir at room temperature. Add acetyl chloride (1.16 mL, 16.2 mmol) and allow the mixture to stir overnight at room temperature. Concentrate the mixture and partition the residue between aq $NaHCO_3$ and EtOAc. Dry the combined extracts over Na_2SO_4 before concentrating. Chromatograph the residue over silica gel ($MeOH/CH_2Cl_2$) which allows for the isolation of 5-[4-(2-acetylamino-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester as an oil that solidifies upon standing (3.51 g, 75 %). MS(ES): $(M+1)^+$ 317.2 m/z.

Example 70

5-[4-(2-acetylamino-phenyl)-oxazol-2-yl]-pentanoic acid



Combine 5-[4-(2-acetylamino-phenyl)-oxazol-2-yl]-pentanoic acid methyl ester (Preparation 60, 3.26 g, 10.3 mmol) with THF (3 mL), EtOH (3 mL) and 1 N NaOH (40 mL) and stir at room temperature until hydrolysis is complete. Concentrate the mixture and dilute the residue with water before adjusting to pH 3.5-4.0 with aq HCl. Extract the mixture with 1-2%MeOH/EtOAc and concentrate the combined extracts in vacuo. Chromatograph the resulting residue over silica gel ($MeOH/CH_2Cl_2$) which allows for isolation of 5-[4-(2-acetylamino-phenyl)-oxazol-2-yl]-pentanoic acid (2.76 g, 89%) as an off white solid. MS(ES): $(M-1)^-$ 301.2, 302.3.

Formulation

Because the compound of formula I may contain a basic and/or acidic moiety (i.e., amino and/or carboxylic acid), said compound may be formulated as a pharmaceutical salt, e.g., as the sodium or hydrochloride salt or as a salt described in "Handbook of Pharmaceutical Salts: Properties, Selection and Use", Weinheim, New York: VHCA; Wiley-VCH, 2002. The compound of formula I is preferably formulated in a dosage unit

form, i.e., in an individual delivery vehicle, for example, a tablet or capsule, prior to administration to the recipient patient. The term "patient" includes humans and non-human animals such as companion animals (dogs, cats, horses and the like). The preferred patient of treatment is a human. Therefore, yet another embodiment of the present invention is a pharmaceutical composition comprising a compound of formula I, or a pharmaceutical salt thereof, an active agent, and a pharmaceutical carrier. The term "pharmaceutical" when used herein as an adjective means substantially non-deleterious to the recipient patient.

The present pharmaceutical compositions are prepared by known procedures using well-known and readily available ingredients. In making the formulations of the present invention, the delivery agent (formula I compound) will be mixed with a GLP-1 compound and will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

Biological Assays

Carrier Formulation Development

For oral dosing, a pH range of 7.4 to 8.4 for each formulation is considered acceptable, with a target carrier concentration of 150 mg/mL. Initial feasibility studies were conducted to determine final carrier formulations.

Briefly, 200 mg of each compound is weighed into a Type I glass vial, to which 1 mL of MilliQ water is added. Each product is visually inspected for solubility, followed by addition of NaOH to increase solubility or HCl to decrease the pH to the oral dose range. Formulations are then diluted to 150 mg/mL with MilliQ water. Using this approach, the formulations generally fell into three categories: aqueous soluble, nearly completely soluble (e.g., few undissolved particles remaining, very fine aqueous suspensions or hazy suspensions), and aqueous insoluble (e.g., heavy suspensions). Compounds that exhibited aqueous insolubility are formulated in 4% w/v (aqueous) hydroxypropylcellulose (Klucel® LF, Hercules, Wilmington, DE) as needed. In these cases, between 50 and 100 mg of compound is suspended in Klucel® LF in a Type I glass vial, to yield a concentration of 200 mg/mL. For heavy aqueous and Klucel® LF suspensions, the preparations are cooled on ice for 3 minutes, followed by probe sonication on ice for 30 minutes using a Misonix Sonicator ® Ultrasonic Processor XL ($3/16^{th}$ inch microtip) to reduce particle size. Following pH adjustment with NaOH or HCl, the formulations are then diluted to 150 mg/mL with MilliQ water or Klucel® LF.

Formulation of Stock Val^{8}-Glu^{22}-GLP-1(7-37)OH Solution

The GLP-1 analog (Val^{8}-Glu^{22}-GLP-1(7-37)OH) used herein has been described in PCT application number PCT/US03/03111. A stock solution of Val^{8}-Glu^{22}-GLP-1(7-37)OH is prepared as follows. Briefly, a known quantity of lyophilized Val^{8}-Glu^{22}-GLP-1(7-37)OH is weighed into a Type I glass vial. MilliQ water is then added to yield an initial concentration of about 7-10 mg/mL. Complete solubility of the peptide is achieved by slowly raising the pH of the medium to 10.5 with 1 N NaOH and 5 N NaOH, followed by incubation at room temperature for 30 minutes. A volume of 1 M Tris buffer, pH 8.0 is added to give a final buffer concentration of 20 mM Tris, and the pH

adjusted to pH 7.8 with 1N HCl and 5 N HCl. The solution is then filtered through a low protein binding 0.22 μM syringe filter (Millex GV, Millipore). The concentration of the peptide filtrate is determined by UV spectroscopy (λ max = 280 nm; light scatter correction applied between 250 nm and 410 nm). The solution is then diluted to a stock concentration of about 5.0 mg/mL using 20 mM Tris buffer, pH 7.8. The peptide solution is stored in 1.0 mL aliquots at -70°C until used.

Rat Oral Delivery Method

Male Sprague-Dawley (femoral artery cannulated, Charles River, Wilmington, MA) rats weighing 250-300 g are used in these studies. Animals are housed in single house stainless steel cages and cared for according to Eli Lilly and Company Animal Care and Use Policies & Procedures. Animals are fasted for at least 12 hours (with free access to water) before dose administration. Each experiment (test compound + peptide [Val^{8}-Glu^{22}-GLP-1(7-37)OH]) is conducted in a group of four rats. Final formulations for each test compound are freshly prepared approximately 5-10 minutes prior to *in vivo* dosing. Specifically, test compound formulation (~165 mg/mL stock) and peptide solution (~ 5.0 mg/mL stock) are added together to yield an admixture of test compound + peptide. The final concentrations of test compound and peptide in each formulation are 150 mg/mL and 0.5 mg/mL, respectively. Formulations are dosed by oral gavage (PO) for a final dose of 300 mg/kg carrier and 1.0 mg/kg peptide. One mL of blood samples is collected in EDTA tubes from the systemic (femoral artery) cannula from each animal (one sample/time point) at 5, 10, and 20 minutes. Tubes are chilled on ice immediately following collection and centrifuged at approximately 5°C/3,000 rpm/15 minutes. Plasma is removed, transferred into 12 x 75 mm polypropylene sample tubes with snap caps, and stored immediately at -70°C until analyzed by a radioimmunoassay.

Radioimmunoassay and Pharmacokinetic analysis

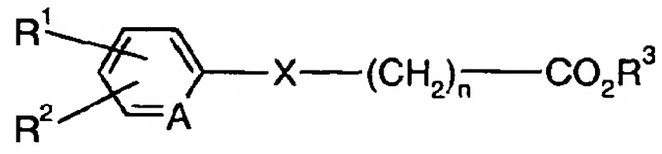
Concentrations of immunoreactive Val^{8}-Glu^{22}-GLP-1(7-37)OH in rat plasma are assayed by a radioimmunoassay assay that non-specifically detects native peptide and metabolic products. These concentrations are subsequently used to determine the reported pharmacokinetic parameters. Plasma samples are mixed with radiolabeled

[^{125}I]-Val^{8}-Glu^{22}-GLP-1(7-37)OH and rabbit polyclonal antiserum and then incubated overnight at ~4°C. Bound and free forms of immunoreactive Val^{8}-Glu^{22}-GLP-1(7-37)OH are separated by precipitating the bound fraction by polyethylene glycol-assisted, secondary antibody precipitation. After collecting the bound fraction by centrifugation, the radioactivity is measured by a gamma counter. Data is analyzed by a weighted 4/5 parameter logistic algorithm. The standard curve ranges from 9.8 pg/mL to 10000 pg/mL. The upper and lower quantification limits are 150 pg/mL and 4000 pg/mL, respectively. Pharmacokinetic analysis is performed using WinNonlin™ Version 3.0 (Pharsight Corporation, Mountain View, CA). Plasma concentration time data are reported as mean ± standard deviation (SD). Carrier efficiency is defined as area under the plasma concentration-time curve measured from 0 to 20 min (AUC) of Val^{8}-Glu^{22}-GLP-1(7-37)OH in the presence of each test compound normalized to AUC of Val^{8}-Glu^{22}-GLP-1(7-37)OH in the presence of the positive control delivery agent 8-[(2-hydroxy-4-methoxy benzoyl) amino]-octanoate disodium salt (US 6,313,088 and WO 01/44199) (Relative AUC).

Representative compounds of formula I were tested with Val^{8}-Glu^{22}-GLP-1(7-37)OH in the Rat Oral Delivery assay and the peptide Val^{8}-Glu^{22}-GLP-1(7-37)OH was detected in the blood. When Val^{8}-Glu^{22}-GLP-1(7-37)OH was administered in the absence of a test compound, the peptide was not detected in the blood.

WE CLAIM:

1. A compound of formula I



I

wherein

R^1 and R^2 are each independently H, OH, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, halo or $NR^4R^{4'}$;

R^3 is H, C_1-C_6 alkyl;

R^4 is H, COR^5, SO_2R^6, or C_1-C_6 alkyl;

$R^{4'}$ is H or C_1-C_6 alkyl;

R^5 is H or C_1-C_6 alkyl;

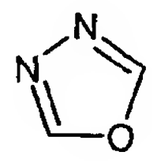
R^6 is H or C_1-C_6 alkyl;

A is C or N;

X is a 5 membered aromatic heterocycle wherein said heterocycle contains at least two or three heteroatoms selected from N, S and O and wherein at least one heteroatom must be N;

n is 2, 3, 4, 5, 6 or 7;

provided that when X is

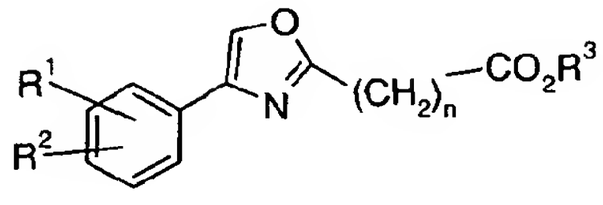


,

then A is N;

or a pharmaceutical salt thereof.

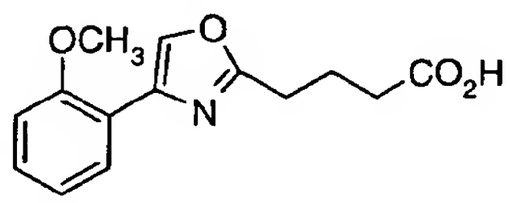
2. A compound of claim 1 wherein compound is of the formula



or a pharmaceutical salt thereof.

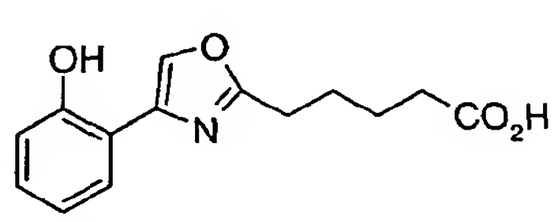
3. A compound of claim 2 wherein R^1 and R^2 are each independently H, $O(C_1\text{-}C_4$ alkyl), OH, R^3 is H and n is 2, 3, 4 or 5, or a pharmaceutical salt thereof.

4. A compound which is



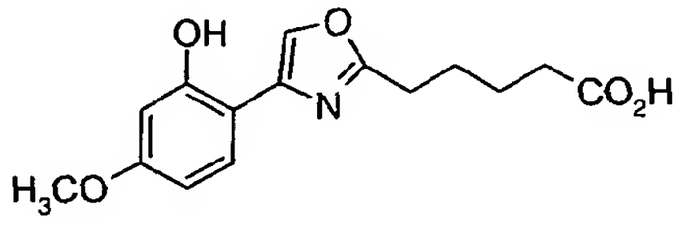
or a pharmaceutical salt thereof.

5. A compound which is



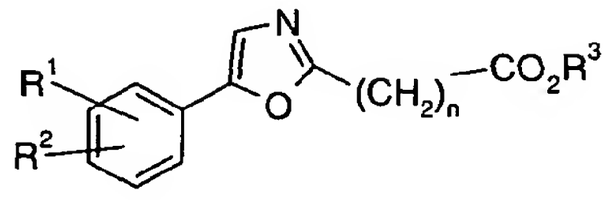
or a pharmaceutical salt thereof.

6. A compound which is



or a pharmaceutical salt thereof.

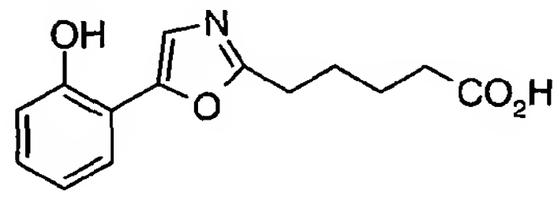
7. A compound of claim 1 wherein compound is of the formula



or a pharmaceutical salt thereof.

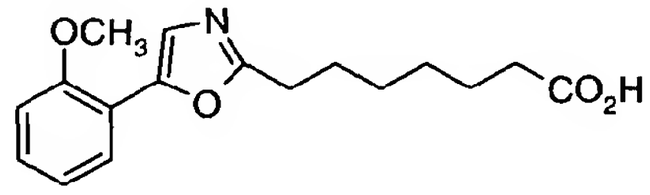
8. A compound of claim 7 wherein R^1 and R^2 are each independently H, $O(C_1\text{-}C_4$ alkyl), OH, R^3 is H and n is 3, 4, 5, 6 or 7, or a pharmaceutical salt thereof.

9. A compound which is



or a pharmaceutical salt thereof.

10. A compound which is



or a pharmaceutical salt thereof.

11. A composition comprising:

a) a compound of any one of claims 1-10 or a pharmaceutical salt thereof; and

b) a GLP-1 compound.

12. A formulation comprising:

a) a compound of any one of claims 1-10 or a pharmaceutical salt thereof;

b) a GLP-1 compound; and

c) a pharmaceutical carrier.

ABSTRACT

The present invention relates to novel compounds, methods, and formulations useful for the oral delivery of a GLP-1 compound.